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Attorneys for Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB

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CASHIERS

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PFIZER INC., PHARMACIA & UPJOHN COMPANY LLC, and PFIZER HEALTH AB,

Plaintiffs,

v.

IMPAX LABORATORIES, INC.,

Defendant.

COMPLAINT

Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB (collectively, "Pfizer"), by their attorneys, White & Case LLP, for their Complaint against Defendant Impax Laboratories, Inc., allege:

THE PARTIES

1. Plaintiff Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York.

2. Plaintiff Pharmacia & Upjohn Company LLC is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 7000 Portage Road, Kalamazoo, Michigan. Pfizer Inc. is the ultimate parent of Pharmacia & Upjohn Company LLC.

3. Pfizer Health AB is a company organized and existing under the laws of Sweden, having a place of business at SE-112 87, Stockholm, Sweden. Pfizer Inc. is the ultimate parent of Pfizer Health AB.

4. Upon information and belief, Impax Laboratories, Inc. ("Impax") is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 30831 Huntwood Avenue, Haywood, California.

JURISDICTION AND VENUE

5. This Court has exclusive subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

6. This court has personal jurisdiction over Impax by virtue of, inter alia: (1) its presence in New York, (2) its systematic and continuous contacts with New York, including its substantial and ongoing sale of generic drugs in New York; and (3) its prior consent to personal jurisdiction in this judicial district.

7. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

U.S. Patent No. 5,382,600

8. On January 17, 1995, the United States Patent and Trademark Office issued United States Patent No. 5,382,600 (the "'600 patent"), entitled "3,3-Diphenylpropylamines and Pharmaceutical Compositions Thereof." At the time of its issue, the

'600 patent was assigned to Pharmacia Aktiebolag. Pfizer Health AB currently holds title to the '600 patent. A copy of the '600 patent is attached hereto as Exhibit A.

9. The '600 patent is directed to and claims, inter alia, 3,3 diphenylpropylamino derivatives and pharmaceutical derivatives thereof, including tolterodine tartrate.

U.S. Patent No. 6,630,162

10. On October 7, 2003, the United States Patent and Trademark Office issued United States Patent No. 6,630,162 (the "'162 patent"), entitled "Pharmaceutical Formulation and its Use." At the time of its issue, the '162 patent was assigned to Pharmacia AB. Pfizer Health AB currently holds title to the '162 patent. A copy of the '162 patent is attached hereto as Exhibit B.

11. The '162 patent is directed to and claims, inter alia, a pharmaceutical formulation for administering tolterodine or tolterodine-related compounds, and the medical use of such a formulation.

U.S. Patent No. 6,770,295

12. On August 3, 2004, the United States Patent and Trademark Office issued United States Patent 6,770,295 (the "'295 patent"), entitled "Therapeutic Formulation for Administering Tolterodine with Controlled Release." At the time of its issue, the '295 patent was assigned to Pharmacia & Upjohn AB. Pfizer Health AB currently holds title to the '295 patent. A copy of the '295 patent is attached hereto as Exhibit C.

13. The '295 patent is directed to and claims, inter alia, an improved method of treating unstable or overactive bladder as well as a formulation therefor.

Detrol LA®

14. Pharmacia & Upjohn Company LLC holds an approved New Drug Application (the "Detrol LA NDA") for tolterodine tartrate extended release capsules, in 2 and 4 mg dosages, which are sold by Pfizer Inc. under the trade name Detrol LA®.

15. Pursuant to 21 U.S.C. § 355(b)(1), and attendant United States Food and Drug Administration ("FDA") regulations, the '600, '162, and '295 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" with respect to Detrol LA®.

Impax's ANDA

16. Impax submitted Abbreviated New Drug Application No. 90-235 (the "Impax ANDA") to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market tolterodine tartrate extended release capsules in a 4 mg dosage form (the "Impax Product").

17. The Impax ANDA refers to and relies upon the Detrol LA NDA and contains data that, according to Impax, demonstrates the bioequivalence of the Impax Product and Detrol LA®.

18. On or about January 31, 2008, Pfizer received from Impax a letter and attached memorandum, dated January 29, 2008 (collectively, the "Impax Notification"), stating that Impax had included in its ANDA a certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that each of the '600, '162, and '295 patents is invalid, unenforceable, or would not be infringed by the manufacture, use, or sale of the Impax Product (the "Paragraph IV Certification").

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 5,382,600

19. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-18 of this Complaint.

20. Impax has infringed the '600 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting ANDA No. 90-235, by which Impax seeks approval from the FDA to engage in the commercial manufacture, use, or sale of the Impax Product prior to the expiration of the '600 patent.

21. If Impax commercially makes, uses, offers to sell, or sells the Impax Product within the United States, or imports the Impax Product into the United States, or induces or contributes to any such conduct during the term of the '600 patent, it would further infringe the '600 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

22. Pfizer will be irreparably harmed if Impax is not enjoined from infringing the '600 patent. Pfizer does not have an adequate remedy at law.

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 6,630,162

23. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-18 of this Complaint.

24. Impax has infringed the '162 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting ANDA No. 90-235, by which Impax seeks approval from the FDA to engage in the commercial manufacture, use, or sale of the Impax Product prior to the expiration of the '162 patent.

25. If Impax commercially makes, uses, offers to sell, or sells the Impax Product within the United States, or imports the Impax Product into the United States, or induces or contributes to any such conduct during the term of the '162 patent, it would further infringe

the '162 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

26. Pfizer will be irreparably harmed if Impax is not enjoined from infringing the '162 patent. Pfizer does not have an adequate remedy at law.

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 6,770,295

27. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-18 of this Complaint.

28. Impax has infringed the '295 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting ANDA No. 90-235, by which Impax seeks approval from the FDA to engage in the commercial manufacture, use, or sale of the Impax Product prior to the expiration of the '295 patent.

29. If Impax commercially makes, uses, offers to sell, or sells the Impax Product within the United States, or imports the Impax Product into the United States, or induces or contributes to any such conduct during the term of the '295 patent, it would further infringe the '295 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

30. Pfizer will be irreparably harmed if Impax is not enjoined from infringing the '295 patent. Pfizer does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB pray for a judgment in their favor and against Defendant Impax Laboratories, Inc. ("Impax"), as follows:

A. That Impax has infringed U.S. Patent No. 5,382,600;

B. That Impax has infringed U.S. Patent No. 6,630,162;

C. That Impax has infringed U.S. Patent No. 6,770,295;

D. That, pursuant to 35 U.S.C. § 271(e)(4)(B), Impax, its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from making, using, selling, offering to sell the Impax Product within the United States, or importing the Impax Product into the United States prior to the expiration of the '600, '162, and '295 patents;

E. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 90-235 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the latest of the expiration dates of the '600, '162, and '295 patents, including any extensions;

F. That Plaintiffs be awarded monetary relief if Impax commercially makes, uses, sells, or offers to sell the Impax Product within the United States, or imports the Impax Product into the United States, prior to the expiration of any of the '600, '162, '295 patents, including any extensions, and that any such monetary relief be awarded to Plaintiffs with prejudgment interest;

G. That Plaintiffs be awarded reasonable attorneys' fees, costs, and expenses because this is an exceptional case under 35 U.S.C. § 285; and

H. That Plaintiffs be awarded such other relief as the Court deems just and proper.

Dated: March 4, 2008
New York, NY

Respectfully submitted,

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EXHIBIT A

US005382600A

United States Patent [19]

Jönsson et al.

[11] Patent Number: 5,382,600

[45] Date of Patent: Jan. 17, 1995

[54] **3,3-DIPHENYLPROPYLAMINES AND PHARMACEUTICAL COMPOSITIONS THEREOF**

[75] Inventors: **Nils A. Jönsson**, Södertälje; **Bengt A. Sparf**, Trångsund; **Lembit Mikiver**, Järna; **Pinchas Moses**, Saltsjö-Boo; **Lisbet Nilvebrant**, Bromma; **Gunilla Glas**, Spånga, all of Sweden

[73] Assignee: **Pharmacia Aktiebolag**, Uppsala, Sweden

[21] Appl. No.: **810,185**

[22] Filed: **Dec. 19, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 543,767, Sep. 24, 1990, abandoned.

[30] **Foreign Application Priority Data**

Jan. 22, 1988 [SE] Sweden 8800207-6

[51] **Int. Cl.**[6] **A61K 31/135**; A61K 31/165; A61K 31/18; C07C 217/62

[52] **U.S. Cl.** **514/603**; 514/620; 514/648; 564/86; 564/165; 564/316

[58] **Field of Search** 564/86, 165, 316; 514/603, 620, 648

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,446,901 5/1969 Jones 424/330

FOREIGN PATENT DOCUMENTS

111894 3/1969 Denmark .
1169944 11/1969 United Kingdom .
1169945 11/1969 United Kingdom .

OTHER PUBLICATIONS

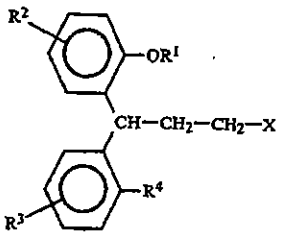
Markaryan et al., Chemical Abstracts, vol. 97 (1982) 120105n.

Atwal et al., J. Med. Chem., vol. 30 (1987) pp. 627–365.

Strehlke et al., Chemical Abstracts, vol. 91 (1979) 107943r.

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Pollock, Vande Sande & Priddy

[57] **ABSTRACT**



(I)

Novel 3,3-diphenylpropylamines of formula (I) wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group $-NR^5$, R^6, wherein R^5 and R^6 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and which may form a ring together with the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers, their use as drugs, especially as anticholinergic agents, their use for preparing an anticholinergic drug, pharmaceutical compositions containing the novel amines, and methods for preparing the same.

7 Claims, No Drawings

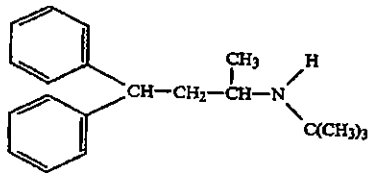
3,3-DIPHENYLPROPYLAMINES AND PHARMACEUTICAL COMPOSITIONS THEREOF

This is a continuation of Ser. No. 07/543,767, filed on Sep. 24, 1990, now abandoned.

The present invention relates to novel 3,3-diphenylpropylamino derivatives, to pharmaceutical compositions containing the same, and to the use of said derivatives for preparing drugs.

Swedish Pat. No. 215 499 discloses certain 3,3-diphenylpropylyamines having an advantageous effect on the heart and circulation. These pharmacologically active 3,3-diphenylpropylamines are secondary amines. Said Swedish patent also discloses certain chemical intermediates which are tertiary amines carrying aromatic substituents on the amine nitrogen. Neither the end products (secondary amines) nor the intermediates (tertiary amines) have any hydroxy or methoxy groups as substituents in the ortho positions of the phenyl rings, but only meta and para substituents are specifically disclosed.

It is known that terodiline, a commercially available drug having the chemical formula

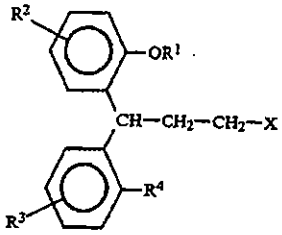


has anti-cholinergic properties, and is well resorbed in the body. However, this drug has a very long biological half-life and it is a multi-effect drug also having other pharmacological properties such as Ca-antagonist, noradrenaline antagonist and anti-histamine properties as well as a pronounced effect on the heart.

U.S. Pat. No. 3,446,901, GB-A-1.169.944 and GB-A-1.169.945 disclose certain 3,3-diphenylpropylamine derivatives and pharmaceutical compositions having antidepressant activity, i.a. N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, which is considered to be the closest prior art as regards chemical structure (see also the comparative tests reported at the end of this specification). DK-A-111.894 discloses a special process for preparing certain diphenylalkylamines having an effect on the heart and circulation. The specifically described compounds are primary or secondary amines, and none of them has any hydroxy or alkoxy substituent in ortho position of the phenyl rings. C.A. Vol. 97(1982) 120105n discloses certain N-arylaklylisoquinolines which may have a hydroxy substituent in the ortho position of a phenyl ring. These compounds have sympatholytic activity and carry aromatic substituents on the nitrogen atom.

It is object of the present invention to provide a novel class of 3,3-diphenylpropylamines having improved anti-cholinergic properties, especially in relation to the effects on these other systems and acute toxicity.

In a first aspect the invention provides novel 3,3-diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II

II

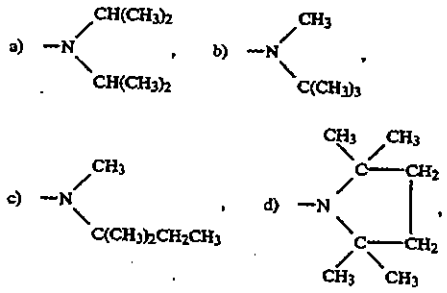
wherein R^5 and R^6 signifky non-aromatic hydrocarbol groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four carbon atoms, especially at least five carbon atoms, and where R^5 and R^6 may form a ring together with the amine nitrogen, said ring preferably having no other hetero atom that the amine nitrogen.

The compounds of formula I can form sales with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

When the novel compounds can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

A preferred sub-class of compounds according to the invention comprises tertiary amines of formula I, wherein each of R^5 and R^6 independently signifies C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms. R^5 and R^6 may carry one or more hydroxy groups, and they may be joined to form a ring together with the amine nitrogen atom.

Presently preferred tertiary amino-groups X in formula I include the following groups a)–f), each of which may carry one or more hydroxy groups.



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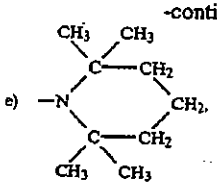
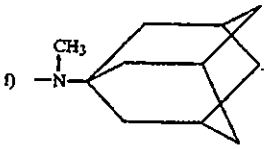
e) 

f) 

The following are examples of presently preferred specific compounds of formula I:

N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and its (+)-isomer,

N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)-propylamine,

N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine,

N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

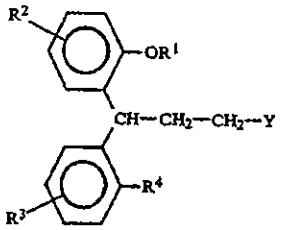
N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

N,N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine,

N-(3-(2-methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine

In a second aspect the invention provides methods for preparing the compounds of formula I, especially the following methods:

a) reacting a reactively esterified 3,3-diphenylpropanol of formula III



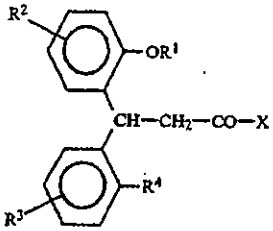
III

wherein R^1–R^4 are as defined above, and any hydroxy groups may be protected such as by methylation or benzylation, and wherein Y is a leaving group, preferably halogen or an alkyl or arylsulphonyloxy group, with an amine of formula IV

IV

wherein X is as defined above, or

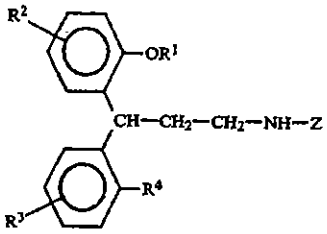
b) reducing a 3,3-diphenylpropionamide of formula V



V

wherein R^1–R^4 and X are as defined above and any hydroxy groups may be protected, preferably using a complex metal hydride,

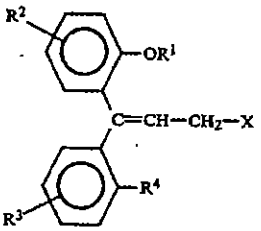
c) N-methylating a secondary 3,3-diphenylpropylamine VI



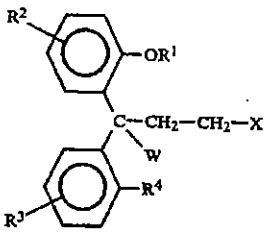
VI

wherein R^1–R^4 are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^5 and R^6 with the exception of methyl, Z preferably being a hydrocarbyl group comprising at least three carbon atoms, the N-methylation preferably being carried out using formaldehyde or formic acid, or

d) reducing a 3,3-diphenylpropylamine of formula VIIa or VIIb



VIIa



VIIb

wherein R^1–R^4 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, preferably by means of catalytic hydrogenation, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono or di-halogenation of one or both of the phenyl rings, and/or

ii) if desired converting obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or

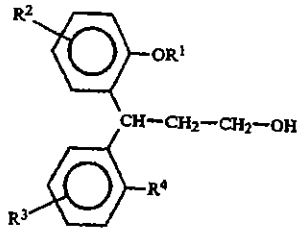
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^4 is hydroxy.

The above general methods can be carried out in a manner known per se and/or in accordance with the working examples described below, with due consideration of the desired amino groups and the substituents on the benzene rings.

The removal of hydroxy protecting groups according to i) above can e.g. be done by treatment with hydrobromic acid, borontribromide or by catalytic hydrogenation.

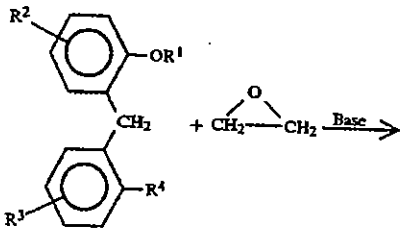
The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

Novel compounds of formula VIII



VIII

wherein R^1–R^4 are as defined above, and the corresponding protected compounds (e.g. comprising protected hydroxy groups), are useful as chemical intermediates for the preparation of e.g. the compounds of formula I, and they can be prepared by means of several different methods which are known per se, such as by addition of ethylene oxide (X) to a correspondingly substituted diphenylmethane (IX) in the presence of a suitable base such as sodium amide:



IX X

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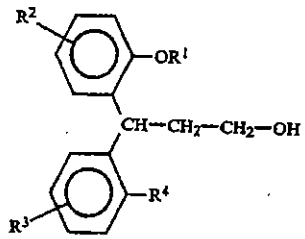


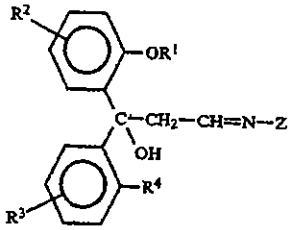
VIII

The compounds VIII can also be prepared by reduction of the corresponding 3,3-diphenylpropionic acids, preferably using complex metal hydrides.

The 3,3-diphenylpropanols VIII can conveniently be converted into the corresponding reactively esterified derivatives III in a manner known per se by displacing the hydroxy groups with e.g. a halogen atom or an alkyl or arylsulphonyloxy group.

The 3,3-diphenylamides of formula V used as starting materials in method b), can e.g. be prepared by reacting the above mentioned 3,3-diphenylpropionic acids with an appropriate amine.

The secondary amines used as starting materials in method c) can conveniently be prepared by reacting a primary amine H_2N-Z (wherein Z is as defined above) with a corresponding reactively esterified 3,3-diphenylpropanol in analogy with method a) above, or by reduction of the corresponding secondary 3,3-diphenylpropionamides in analogy with method b) above. The secondary amines can also be prepared by reduction of unsaturated hydroxyamines XI



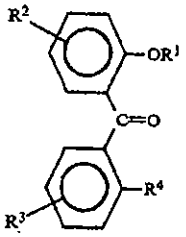
XI

wherein R^1–R^4 and Z are as defined above, either in one step by catalytic hydrogenation, or by reduction to the corresponding saturated hydroxyamine, preferably using a complex metal hydride such as lithium aluminium hydride, followed by removal of the hydroxy group by catalytic reduction. As an alternative, the hydroxy group may first be split off as water, followed by reduction of the formed unsaturated amine.

The unsaturated hydroxy amines XI can conveniently be prepared by the addition of a Schiff base of formula XII

XII

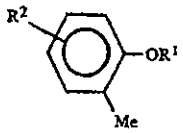
wherein Z is as defined above, to a benzophenone of formula XIII



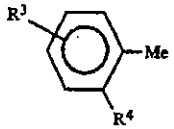
XIII

wherein R^1–R^4 are as defined above, in the presence of a base, preferably a lithium organic base such as lithium diisopropylamide.

Also the starting materials VIIa, VIIb for process d) can be prepared by methods known per se, such as by addition of an organometallic compound XIVa or XIVb

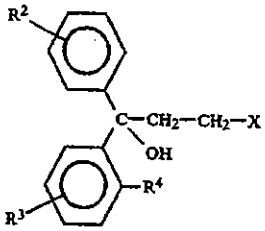


XIVa



XIVb

to a ketoamine XVa or XVb respectively to form a corresponding hydroxy amine XVI



XVI

and, if desired, splitting off water from compound XVI.

In formulae XIVa, XIVb, XVa, XVb, XVI, R^1–R^4 are as defined above, and Me signifies a metal such as magnesium or lithium.

In accordance with the invention the compounds of formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise the compounds of formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds and compositions according to the invention can be used for treating cholin-mediated disorders such as urinary incontinence. As is well known, the dosage depends on several factors such as the potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. The daily dosage may, for example, be from about 0.05 mg to about 4 mg per kilo of body weight, administered in one or more doses, e.g. containing from about 0.05 to about 200 mg each.

The invention will be further illustrated by the following non-limiting examples.

General

^{1}H-NMR spectra were run in $CDCl_3$ using a JEOL PMX60 spectrometer. In some cases, only a limited number of spectral peaks, useful for characterization purposes, are reported.

Reported yields mostly refer to crude material of sufficient purity to be taken to the next stage.

Solvents are abbreviated as follows:
IPE=diisopropyl ether
PET=petroleum ether
Ether=diethyl ether

Amines are abbreviated as follows:
IPA=diisopropyl amine
TBA=tert.butyl amine

Melting points were taken on a Koefler bench.

Temperatures are in °C.

Water is used for the washing steps, unless otherwise stated.

EXAMPLE 1

Preparation of 4-phenyl-3,4-dihydrocoumarins

a) 4-(2-Methoxy-5-methylphenyl)-6-methyl-3,4-dihydrocoumarin (I)

A mixture consisting of 2-methoxy-5-methylcinnamic acid (96.0 g, 0.5 mol), p-cresol (108 g, 1.0 mol), tetraline (200 ml), and conc. sulphuric acid (20 g) was heated slowly to refluxing temperature (145°–150°). After 1½–2 h, the mixture was cooled, taken up in ether, washed with water and sodium carbonate, dried and evaporated, giving 138 g (97%) crude oil. Two recrystallisations from acetone gave white crystals of the desired lactone, m.p. 126°–127°.

$C_{18}H_{18}O_3$ (282.3) requires: C, 76.57; H, 6.43; O, 17.00, Found: C, 76.9; H, 6.44; O, 17.0.

b) 6-Hydroxy-4-phenyl-3,4-dihydrocoumarin (II) was prepared in a similar way in 97% yield from cinnamic acid and hydroquinone. M.p. 138° (IPE-Ether).

$C_{15}H_{12}O_3$ (240.3) requires: C, 74.99; H, 5.04; O, 19.98, Found: C, 75.0; H, 5.00; O, 19.6.

c) 4-(2-Methoxy-4-methylphenyl)-7-methyl-3,4-dihydrocoumarin was obtained in a similar way from 2-methoxy-4-methylcinnamic acid and m-cresol in 58% yield. M.p. 147°–148° (IPE-acetone).

$C_{18}H_{18}O_3$ (282.3) requires: C, 76.57; H, 6.43; O, 17.00, Found: C, 76.4; H, 6.31; O, 17.2.

The above lactone (90 g, 0.32 mol) in methylene chloride (500 ml) was refluxed with BBr_3 (115 g, 0.46 mol) for 24 h, the solution was concentrated, the residue was taken up in ether, the solution was washed with sodium carbonate and water, dried and evaporated,

giving 80 g (93%) of a syrup which crystallized on standing. Crystallization from IPE-PET gave white crystals of

d) 4-(2-hydroxy-4-methylphenyl)-7-methyl-3,4-dihydrocoumarin (III), m.p. 137°.

$C_{17}H_{16}O_3$ (268.3) requires: C, 76.10; H, 6.01; O, 17.89, Found: C, 76.2; H, 6.30; O, 17.0.

e) 8-Hydroxy-4-phenyl-3,4-dihydrocoumarin (IV) was obtained in a similar way from cinnamic acid and catechol in 18% yield. M.p. 136° (IPE).

$C_{15}H_{12}O_3$ (240.2) requires: C, 74.99; H, 5.04; O, 19.98, Found: C, 75.0; H, 5.01; O, 19.9.

f) 4-(2-Methoxyphenyl)-3,4-dihydrocoumarin (V) was obtained in a similar way in 45% yield from methyl 2-methoxycinnamate and phenol. The crude reaction mixture was contaminated with methyl 3-(4-hydroxyphenyl)-3-(2-methoxyphenyl)-propionate. After removal of this by-product with ice-cold NaOH, the title compound was obtained as an oil of sufficient purity to be taken to the next step.

EXAMPLE 2

Preparation of 3,3-diphenylpropionic acid esters

a) Methyl 3-(2-methoxy-4-methylphenyl)-3-phenylpropionate (VI)

7-Methyl-4-phenyl-3,4-dihydrocoumarin (78 g, 0.327 mol) in 150 ml methanol and 150 ml acetone containing methyl iodide (100 g, 0.7 mol) and K_2CO_3 (55 g, 0.4 mol) was refluxed for 24 h, filtered, and the solvent was evaporated. The residue was dissolved in ether, the solution was washed with water, dried and evaporated giving 86 g (92%) of a viscous oil.

NMR: δ 6.6–7.2 (m 8H), 4.9 (t 1H), 3.8 (s 3H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 3H).

b) Methyl 3,3-bis-(2-methoxyphenyl)-propionate (VII) was obtained in the same way in 96% yield from the lactone (V) of Example 1f), m.p. 84°–87° (IPE).

$C_{18}H_{20}O_4$ (300.4) requires: C, 71.98; H, 6.71; O, 21.3, Found: C, 71.4; H, 6.67; O, 21.6.

c) Methyl 3-(2,3-dibenzyloxyphenyl)-3-phenylpropionate (VIII) was obtained in a similar way in quantitative yield from the lactone (IV) of Example 1e) and benzyl chloride in methanol. In addition to K_2CO_3 the reaction mixture also contained some NaI. M.p. 72° (IPE).

$C_{30}H_{28}O_4$ (452.5) requires: C, 79.63; H, 6.24; O, 14.14, Found: C, 79.9; H, 6.15; O, 14.1.

d) Methyl 3-(2-benzyloxyphenyl)-3-phenylpropionate (IX) was obtained in a similar way as a viscous oil in 81% yield from 4-phenyl-3,4-dihydrocoumarin and benzyl chloride.

NMR: δ 7.2 (m 14H), 4.9 (s 2H, t 1H), 3.5 (s 3H), 3.0 (t 2H).

e) Methyl 3-(2-methoxy-5-methylphenyl)-3-phenylpropionate (X) was obtained in a similar way from 6-methyl-4-phenyl-3,4-dihydrocoumarin in 96% yield.

NMR: δ 7.4 (m 8H), 5.0 (t 1H), 3.9 (s 3H), 3.7 (s 3H), 3.2 (d 2H), 2.4 (s 3H).

f) Methyl 3,3-bis-(2-methoxy-5-methylphenyl)propionate (XI) was obtained in a similar way in quantitative yield from the lactone (I) of Example 1a) and methyl iodide.

NMR: δ 6.6–7.1 (m 6H), 5.1 (t 1H), 3.7 (s 6H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 6H).

g) Methyl 3-(2,5-dibenzyloxyphenyl)-3-phenylpropionate (XII) was obtained in a similar way in 90% yield from the lactone (II) of Example 1b) and benzyl chloride.

NMR: δ 6.8–7.4 (m 18H), 5.0 (s 4H, t 1H), 3.7 (s 3H), 3.1 (d 2H).

h) Methyl 3,3-bis-(2-benzyloxy-4-methylphenyl)propionate (XIII) was obtained in a similar way in 95% yield from the lactone (III) of Example 1d) and benzyl chloride. By GLC the product is homogenous, and by MS it has the correct M.W.

i) Ethyl 3-(2,4-dimethoxyphenyl)-3-phenylpropionate (XIV)

A mixture of ethyl cinnamate (88 g, 0.5 mol), dimethyl resorcinol (276 g, 2.0 mol) and conc. sulphuric acid (50 g) was stirred on a boiling water-bath for 2 h, whereafter all the volatile material was distilled off in vacuum. The residual oil was dissolved in ether, the solution was washed with sodium carbonate, dried, and evaporated giving 101 g (64%) of the title ester in the form of a viscous oil.

NMR: δ 6.4–7.2 (m 8H), 4.9 (t 1H), 4.0 (q 2H), 3.7 (s 6H), 3.0 (d 2H), 1.1 (t 3H).

j) Methyl 3,3-bis-(2,4-dimethoxyphenyl)propionate (XV) was obtained in a similar way from methyl 2,4-dimethoxycinnamate and dimethyl resorcinol. The product thus obtained contained about 23% of dimethyl resorcinol. It was taken to the next step without further purification.

k) Methyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropionate

6-Chloro-4-phenyl-3,4-dihydrocoumarin (435 g, 1.68 mol. Preparation: T. Manimaran & V. T. Ramakrishnan, Ind. J. Chem. B 18 (1979) 328) is added to a hot solution of sodium hydroxide (140 g, 3.5 mol) in water (500 ml). The solution is chilled to 25° C. and dimethyl sulphate (442 g, 3.5 mol) is added dropwise during 1 h with stirring and cooling at 25°–35° C. The mixture is stirred for an additional 2 h whereupon a solution of 100 g of sodium hydroxide in 500 ml of water is added and the mixture is stirred until a clear solution is obtained. An excess of concentrated hydrochloric acid is added to precipitate the methoxy acid, which separates as an oil which slowly crystallizes. It is filtered off, washed with water and dried. Crystallization from 2-propanol gives colourless crystals of 3-(5-chloro-2-methoxyphenyl)-3-phenyl propionic acid, m.p. 144° C. Yield 455 g.

The above acid (291 g, 1.0 mol) in 1 liter methanol containing 50 g concentrated sulphuric acid was refluxed for 8 h. The solvent was distilled off, the residue was taken up in ether, washed with water and sodium carbonat solution, dried and evaporated giving 300 g (100%) crude oil. Recrystallisation from IPE gave white crystals of the title compound, m.p. 65°–66°.

$C_{17}H_{17}ClO_3$ (304,8) requires: C, 67.0; H, 5.62; Cl, 11.63, Found: C, 68.1; H, 5.82; Cl, 11.7.

EXAMPLE 3

Preparation of 3,3-diphenylpropanols

a) 3-(2-Methoxy-4-methylphenyl)-3-phenylpropanol (XVI)

The ester (VI) of Example 2a) (84 g, 0.295 mol) in 150 ml dry ether was added dropwise to a suspension of $LiAlH_4$ (11.3 g, 0.295 mol) in 300 ml dry ether. The mixture was stirred overnight, then decomposed by the careful addition first of 11 g of water, then of 15% NaOH until a white granular precipitate was formed. The mixture was filtered, the filtrate was washed with

water, dried, and evaporated giving 71 g (91%) of an oil which crystallized on standing. Recrystallization from IPE-PET gave white crystals, m.p. 83°.

$C_{17}H_{20}O_2$ (256.4) requires: C, 79.65; H, 7.88; O, 12.48, Found: C, 79.4; H, 7.89; O, 12.7.

b) 3,3-Bis-(2-methoxyphenyl)propanol (XVII) was obtained in a similar manner in quantitative yield as a viscous oil from the ester (VII) of Example 2b).

c) 3-(2,3-Dibenzyloxyphenyl)-3-phenylpropanol (XVIII) was obtained in a similar way as a viscous oil in 96% yield from the ester (VII) of Example 2c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropanol (XIX) was obtained in a similar was as an oil in 78% yield from the ester (IX) of Example 2d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropanol (XX) was obtained in a similar way as an oil in quantitative yield from the ester (X) of Example 2e).

NMR: δ 6.8–7.4 (m 7H), 4.7 (t 1H), 3.8 (s 3H), 3.7 (m 2H), 2.3 (s 3H), 2.0–2.3 (m 2H).

f) 3,3-Bis-(2-methoxy-5-methylphenyl)propanol (XXI) was obtained in a similar way in 98% yield from the ester (XI) of Example 2f). M.p. 89° (IPE).

$C_{19}H_{24}O_3$ (300.4) requires: C, 75.97; H, 8.05; O, 15.98, Found: C, 75.9; H, 8.02; O, 16.1.

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropanol (XXII) was obtained in a similar way in 88% yield from the ester (XII) of Example 2g). M.p. 78° (IPE).

$C_{29}H_{28}O_3$ (424.5) requires: C, 82.05; H, 6.65; O, 11.31, Found: C, 82.0; H, 6.62; O, 11.2.

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)propanol (XXIII) was obtained in a similar way as an oil in 93% yield from the ester (XIII) of Example 2h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropanol (XXIV) was obtained as a golden oil in 92% yield from the ester (XIV) of Example 2i).

NMR: δ 6.5–7.2 (m 8H), 4.5 (t 1H), 3.8 (s 6H), 3.6 (m 2H), 2.0–2.6 (m 3H).

j) 3,3-Bis-(2,4-dimethoxyphenyl)propanol (XXV) was obtained in a similar way from the impure ester (XV) of Example 2j). By NMR, the product contains about 20% of dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)propanol (XXVI)

A Grignard reagent was prepared in the usual manner from o-bromoanisole (93.5 g, 0.5 mol) and magnesium (12 g, 0.5 mol) in 100 ml dry ether. A solution of p-fluorobenzaldehyde (62 g, 0.5 mol) in 100 ml ether was added dropwise to this solution. After about 1 h, the mixture was decomposed with NH_4Cl and worked up, giving 100.6 g (87%) of 4-fluoro-2'-methoxy-diphenylmethanol. Recrystallization from IPE-PET gave white crystals, m.p. 88°.

$C_{14}H_{13}FO_2$ (232.3) requires: C, 72.40; H, 5.64, Found: C, 72.9; H, 5.75.

The obtained carbinol (46.2 g, 0.2 mol) in 600 ml ethanol was hydrogenated in the presence of 4 g of 5% Pd/C catalyst. After about 5–6 h, the reaction was complete and the mixture was worked up giving 40 g (93%) of 4-fluoro-2'-methoxy-diphenylmethane as a clear oil.

NMR: 6.8–7.2 (m 8H), 4.0 (s 2H), 3.8 (s 3H).

The obtained methane derivative (71 g, 0.33 mol) in 100 ml ether was added to a solution of $NaNH_2$ prepared in situ from sodium (8.5 g, 0.37 mol) in about 300 ml of NH_3. After about 1 h, a solution of ethylene oxide (17.5 g, 0.395 mol) in 75 ml ether was added dropwise. The mixture was stirred for 2 h, and most of the ammonia was then removed with a stream of air. Solid NH_4Cl was then added, followed by the addition of water. The organic phase was separated, washed with water and 2N HCl, dried and evaporated, giving 81.5 g (95%) of the title compound. M.p. 61° (IPE-PET).

$C_{16}H_{17}FO_2$ (260.3) requires: C, 73.82; H, 6.58, Found: C, 74.1; H, 6.77.

l) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropanol

The ester from Example 2k) (91.5 g, 0.3 mol) in 500 ml dry ether was added dropwise under nitrogen to $LiAlH_4$ (11.4 g, 0.3 mol) in 200 ml dry ether. The mixture was stirred at room temperature overnight, then decomposed with 11 g water and 11 g 15% NaOH solution. Work up gave 72.5 g (87.5%) colourless oil. Recrystallization from IPE gave white crystals of the title compound, m.p. 80°.

$C_{16}H_{17}ClO_2$ (276.8) requires: C, 69.43; H, 6.19; Cl, 12.81, Found: C, 70.1; H, 6.44; Cl, 12.9.

EXAMPLE 4

Preparation of 3,3-diphenylpropyl-p-toluene sulphonates

a) 3,3-Bis-(2-methoxyphenyl)propyl-p-toluene sulphonate (XXVII)

The propanol (XVII) of Example 3b) (35 g, 0.128 mol) in 100 ml chloroform containing 30 ml pyridine was cooled to about −10° and then treated with p-toluene sulphonyl chloride (29 g, 0.15 mol). After standing in the cooler (about +5° C.) overnight, the mixture was poured into ice-water, the organic phase was washed with water and cold 2N HCl, dried, and the solvent was distilled off at <50° C., giving a crude oil in quantitative yield. Recrystallization from IPE gave white crystals of low and indefinite m.p.

$C_{24}H_{26}O_5S$ (426.5) requires: C, 67.58; H, 6.14; S, 7.52, Found: C, 66.8; H, 6.22; S, 7.76.

b) 3(2-Methoxy-4-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXI) was obtained in quantitative yield from the propanol (XVI) of Example 3a).

c) 3-(2,3-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXVIII) was obtained in a similar way as a thick oil in 88% yield from the propanol (XVIII) of Example 3c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXIX) was obtained in i similar way in 98% yield from the propanol (XIX) of Example 3d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXX) was obtained in quantitative yield from the propanol (XX) of Example 3e). M.p. 64° (IPE-PET).

$C_{23}H_{24}O_4S$ (396.5) requires: C, 69.67; H, 6.10; S, 8.09, Found: C, 69.8; H, 6.20; S, 7.85.

f) 3,3-Bis-(2-methoxy-5-methylphenyl)-propyl-p-toluene sulphonate (XXXII) was obtained in quantitative yield from the propanol (XXI) of Example 3f). M.p. 117° (acetone-PET).

$C_{26}H_{30}O_5S$ (454.5) requires: C, 68.7; H, 6.65; S, 7.05, Found: C, 68.8; H, 6.66; S, 7.11.

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXIII) was obtained in a similar manner in quantitative yield from the propanol (XXII) of Example 3g).

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)-propyl-p-toluene sulphonate (XXXIV) was obtained in a similar way in 86% yield from the propanol (XXIII) of Example 3h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXV) was in the same way obtained in 96% yield from the propanol (XXIV) of Example 3i).

j) 3,3-Bis-(2,4-dimethoxyphenyl)-propyl-p-toluene sulphonate (XXXVI) was obtained in the same manner from the propanol (XXV) of Example 3j). The product was contaminated with dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)-propyl-p-toluene sulphonate (XXXVII) was obtained in a similar way in 88% yield from the propanol (XXVI) of Example 3k). M.p. 67° (IPE).

$C_{23}H_{23}FO_4S$ (414.5) requires: C, 66.65; H, 5.59; S, 7.74, Found: C, 67.1; H, 5.69; S, 7.78.

l) 3-(2-Methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XLVIII)

A mixture of anisole (1080 g, 10 mol), benzyl alcohol (216 g, 2 mol) and p-toluene sulphonic acid (40 g) was refluxed for 2 h in an apparatus equipped with a water separator. Excess of anisole was then distilled off, the oily residue was dissolved in ether, washed with water and sodium carbonate, dried and fractionated, giving 304 g (77%) of a pale yellow oil, b.p. 115°–118°/0.4 Torr. By NMR, it is a 1:1 mixture of o-methoxy and p-methoxy diphenyl methane. This material was converted to a mixture of the corresponding propanols by reaction with ethylene oxide, as in the preparation of the propanol (XXVI) of Example 3k). This mixture of propanols was then converted as described above to a mixture of p-toluene sulphonates from which the title-compound could be isolated in 35% yield after two recrystallizations from IPE. M.p. 108°.

$C_{23}H_{24}O_4S$ (396.5) requires: C, 69.67; H, 6.10; S, 8.09, Found: C, 69.3; H, 6.00; S, 8.17.

m) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate

The alcohol from Example 3l) (66 g, 0.24 mol) in 300 ml chloroform containing 75 ml pyridine was treated portionswise in the cold with p-toluene-sulphonyl chloride (55 g, 0.29 mol). The mixture was kept at 5° C. for 18 h, solvent was evaporated under vacuum at <50°, the residue was taken up in ether, washed with water and 2N HCl, dried and evaporated giving 100 g (97%) of a straw-yellow syrup. Recrystallization from IPE gave the title compound, m.p. 89°–90°.

$C_{23}H_{23}ClO_4S$ (430.96) requires: C, 64.10; H, 5.38; S, 7.44; Cl, 8.23, Found: C, 64.4; H, 5.45; S, 7.04; Cl, 8.17.

EXAMPLE 5

Preparation of tertiary 3,3-diphenylpropylamines

a) N,N-Diisopropyl-3,3-bis-(2-methoxyphenyl)-propylamine (XXXVIII), hydrogen oxalate

The tosylate (XXVII) of Example 4a) (42.6 g, 0.1 mol) in 100 ml acetonitrile and 100 g (1.0 mol) diisopropylamine was heated in a pressure bottle at 80° for 4–6 days. Volatile material was then evaporated, the residue was treated with excess of 2N NaOH and extracted with ether. The extract was washed with water and extracted with 2N HCl. This extract was washed with ether, basified, extracted with ether, washed with water, dried, decoloured, filtered, and evaporated, giving 24.0 g (68%) of a crude oil. This oil was converted to the oxalic acid salt by treating an acetone solution of the base with one equivalent of oxalic acid in acetone. M.p. 160°–161° (acetone).

$C_{25}H_{35}NO_6$ (445.6) requires: C, 67.39; H, 7.92; N, 3.14; O, 21.55, Found: C, 67.2; H, 8.22; N, 2.94; O, 21.9.

b) N,N-Diisopropyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (XXXIX)

The free base was obtained in the same way in 75% yield from the tosylate (XXVIII) of Example 4c).

NMR: 6.9–7.2 (m 18H), 5.0 (s 4H), 0.9 (d 12H).

c) N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (XL), hydrogenfumarate

The free base was obtained in 69% yield from the tosylate (XXX) of Example 4e). It was converted to the fumaric acid salt in the usual manner. M.p. 176° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires: C, 71.17; H, 8.20; N, 3.07; O, 17.6, Found: C, 71.3; H, 8.27; N, 3.04; O, 17.9.

d) N,N-Diisopropyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (XLI), hydrogenfumarate

The free base was obtained in 25% yield from the tosylate (XXXI) of Example 4b). The fumaric acid salt had m.p. 147°–148° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires: C, 71.17; H, 8.20; N, 3.07; O, 17.6, Found: C, 71.3; H, 8.14; N, 3.00; O, 17.6.

e) N,N-Diisopropyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (XLII), hydrochloride

The free base was obtained in 78% yield from the tosylate (XXXII) of Example 4f). It was converted to the hydrochloride with ethereal HCl in the usual manner. M.p. 163°–164° (acetone-ether).

$C_{25}H_{38}NO_2Cl$ (420.1) requires: C, 71.49; H, 9.12; N, 3.33; O, 7.61; Cl, 8.44, Found: C, 71.6; H, 9.08; N, 3.27; O, 7.93; Cl, 8.36.

f) N,N-Diisopropyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (XLIII)

The free base was obtained in 70% yield from the tosylate (XXXIII) of Example 4g).

NMR: δ 6.6–7.2 (m 18H), 5.0 (s 4H), 4.5 (t 1H), 1.0 (d 12H).

g) N,N-Diisopropyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propylamine (XLIV)

The free base was obtained in 62% yield from the tosylate (XXXIV) of Example 4h).

NMR: δ 6.8–7.2 (m 16H), 4.8 (s 4H, t 1H), 0.9 (d 12H).

h) N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (XLV)

The free base was obtained in 56% yield from the tosylate (XXXV) of Example 4i).

NMR: 6.5–7.3 (m 8H), 4.4 (t 1H), 3.8 (s 6H), 1.0 (d 12H).

i) N,N-Diisopropyl-3,3-bis-(2,4-dimethoxyphenyl)-propylamine (XLVI)

The free base was obtained in 34% yield from the tosylate (XXXVI) of Example 4j).

NMR: δ 6.5–7.3 (m 6H), 4.6 (t 1H), 3.9 (s 12H), 1.0 (d 12H).

j) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)propylamine XLVII)

The free base was obtained in 71% yield from the tosylate (XXXVII) of Example 4k).

k) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine (XLIX), hydrogen fumarate

The free base was obtained in 86% yield from the tosylate (XLVIII) of Example 4l) and was converted to the fumaric acid salt in the usual way. M.p. 134°–136° (acetone-IPE) or 163°–164° (methanol).

$C_{26}H_{36}NO_5$ (441.6) requires: C, 70.72; H, 7.99; N, 3.28; O, 18.12, Found: C, 70.8; H, 7.93; N, 3.28; O, 18.1.

l) N-(3-(2-Methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine (LXIV)

This compound was obtained in the same way in 54% yield from the tosylate (XLVIII) of Example 4l) and 2,2,6,6-tetramethylpiperidine. M.p. 100° (IPE).

$C_{25}H_{35}NO$ (365.6) requires: C, 82.14; H, 9.65; N, 3.83, Found: C, 82.0; H, 9.62; N, 3.57.

m) N,N-diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) was heated for 4 days at 80° with diisopropylamine (50 g, 0.5 mol) in 100 ml acetonitrile, giving 23 g (64%) of crude title compound. By GC, it is at least 93% pure.

n) N-(3-(2-Benzyloxyphenyl)-3-phenylpropyl)-2,2,5,5-tetramethylpyrrolidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2,2,5,5-tetramethylpyrrolidine. It was obtained as a sticky oil, which was converted to the hydroxy analogue without further purification (Example 9ab)).

o) N-(3-(2-Benzyloxyphenyl)-3-phenylpropyl)-4-hydroxy-2,2,6,6-tetramethylpiperidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 4-hydroxy-2,2,6,6-tetramethylpiperidine, and it was obtained as a sticky oil which was converted to the hydroxy compound without further purification (Example 9ac)).

p) N-(2-Hydroxy-1,1-dimethylethyl)-3-(2-benxyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2-amino-2-methylpropanol. The solid product was crystallized from diisopropyl ether and melted at 103° C. It was used as start material in (Example 7p).

$C_{26}H_{31}NO_2$ (389.5) requires: C, 80.17; H, 8.02; N, 3.60; O, 8.22, Found; C, 80.0; H, 8.09; N, 3.69; O, 8.51.

q) N-(1-Adamantyl)-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the toyslate (XXIX) of Example 4d) and 1-aminoadamantane. It was used as start material in Example 7q). The hydrochloridesemihydrate was prepared in acetonitrile and melted at 225° C.

$C_{32}H_{37}NO.HCl.\frac{1}{2}\ H_2O$ (497.1) requires: C, 77.31; H, 7.91; N, 2.82; O, 4.83; Cl, 7.13, Found: C, 77.3; H, 8.23; N, 2.65; O, 5.04; Cl, 7.14.

EXAMPLE 6

Preparation of secondary 3,3-diphenylpropylamines

a) N-tert.Butyl-3,3-bis-(2-methoxyphenyl)propylamine (L), hydrogen oxalate

The tosylate (XXVII) of Example 4a) was heated with a large excess of tert.butylamine as described in Example 5, giving the free base in 78% yield, which was converted to the oxalic acid salt in the usual manner. M.p. 135°–136° (acetone-ether).

$C_{23}H_{31}NO_6$ (417.5) requires: C, 66.17; H, 7.48; N, 3.36; O, 22.99, Found: C, 65.6; H, 7.31N, 3.36; O, 23.4.

b) N-ter.Butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (LI), hydrochloride

The free base was obtained as above in 78% yield from the tosylate (XXVIII) of Example 4c). The HCl salt had m.p. 184°–185° (acetone-methanol-IPE).

$C_{33}H_{38}NO_2Cl$ (516.1) requires: C, 76.79; H, 7.42; N, 2.71; O, 6.20; Cl, 6.87, Found: C, 76.3; H, 7.30; N, 2.72; O, 6.42; Cl, 6.81.

c) N-tert.Butyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine (LII), hydrogen oxalate

The free base was obtained in 84% yield from the tosylate (XXIX) of Example 4d). The oxalic acid salt had m.p. 198° (acetone-ether).

$C_{28}H_{33}NO_5$ (463.6) requires: C, 72.54; H, 7.18; N, 3.02, Found: C, 71.8; H, 7.13; N, 2.95.

d) N-tert.Butyl-3-(2-methoxy-5-methyplenyl)-3-phenylpropylamine (LIII), hydrochloride

The free base was obtained in 90% yield from the tosylate (XXX) of Example 4e). When treated with ethereal HCl, it gave a somewhat hygroscopic salt which seems to be associated with ¼ mol water. Mp. 171° ethanol-ether).

$C_{21}H_{29}NO.HCl.\frac{1}{4}\ H_2O$ (352.5) (requires): C, 71.55; H, 8.74; N, 3.97; O, 5.67; Cl, 10.06, Found: C, 71.8; H, 8.72; N, 4.05; O, 5.57; Cl, 10.1.

e) N-ter.Butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (LIV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXI) of Example 4b). The HCl-salt had m.p. 138°–149° (methanol-isopropanol). It was associated with ¾ mol of water.

$C_{21}H_{30}NOCl.\frac{3}{4}\ H_2O$ (361.5) requires: C, 69.77; H, 8.80; N, 3.88; Cl, 9.81, Found: C, 69.8; H, 8.76; N, 3.93; Cl, 9.75.

f) N-ter.Butyl-3,3-bis-(2-methoxy-5-methylphenyl)-propylamine (LV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXII) of Example 4f). The HCl-salt had m.p. 242° (acetone).

$C_{23}H_{34}NOCl$ (392.0) requires: C, 70.47; H, 8.74; N, 3.57; Cl, 9.05, Found: C, 70.2; H, 8.81; N, 3.46; Cl, 8.99.

g) N-tert.Butyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (LVI), hydrochloride

The free base was obtained in 85% yield from the tosylate (XXXIII) of Example 4g). The HCl salt had m.p. 188° (ethanol-ether).

$C_{33}H_{38}NO_2Cl$ (516.1) requires: C, 76.79; H, 7.42; N, 2.71; O, 6.20; Cl, 6.87, Found: C, 77.2; H, 7.50; N, 2.64; O, 6.53; Cl, 6.85.

h) N-tert.Butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)-propylamine (LVII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXIV) of Example 4h). The HCL-salt had m.p. 210° (acetone-ether).

$C_{35}H_{42}NO_2Cl$ (544.2) requires: C, 77.25; H, 7.78; N, 2.57; O, 5.89; Cl, 6.52, Found: C, 77.6; H, 7.82; N, 2.35; O, 6.08; Cl, 6.55.

i) N-tert.Butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (LVIII), hydrochloride

The free base was obtained in 84% yield from the tosylate (XXXV) of Example 4i). The HCl-salt had m.p. 196° (acetone-ethanol-ether).

$C_{21}H_{30}NO_2Cl$ (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.3; H, 8.44; N, 3.80; O, 8.89; Cl, 9.81.

j) N-tert.Butyl-3,3-bis-(2,4-dimethoxyphenyl)-propylamine (LIX), hydrochloride

The free base was obtained in 60% yield from the tosylate (XXXVI) of Example 4j). The HCl-salt had m.p. 251° (methanol-acetone).

$C_{23}H_{34}NO_4Cl$ (424.0) requires: C, 65.15; H, 8.08; N, 3.30; O, 15.09; Cl, 8.36, Found: C, 64.5; H, 8.06; N, 3.57; O, 15.3; Cl, 8.67.

k) N-tert.Butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)-propylamine (LX), hydrochloride

The free base was obtained in 89% yield from the tosylate (XXXVII) of Example 4k). The HCl-salt had m.p. 194° (ethanol-acetone).

$C_{20}H_{27}NOFCl$ (351.9) requires: C, 68.26; H, 7.73; N, 3.98; Cl, 10.08, Found: C, 68.9; H, 7.97; N, 4.01; Cl, 9.69.

l) N-tert.Butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXI), hydrochloride

The free base was obtained in 88% yield from the tosylate (XLVIII) of Example 4l). The HCl-salt had m.p. 205°.

$C_{20}H_{28}NOCl$ (333.9) requires: C, 71.94; H, 8.45; N, 4.20; O, 4.79, Found: C, 71.9; H, 8.44; N, 4.67; O, 4.79.

m) N-(1,1-Dimethylpropyl)-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXII), hydrochloride

The free base was obtained in 95% yield from the tosylate (XXX) of Example 4e) and tert. amylamine. The HCl-salt had m.p. 188°–189° (ethanol-acetone).

$C_{22}H_{32}NOCl$ (362.0) requires: C, 73.00; H, 8.91; N, 3.87; O, 4.42; Cl, 9.80, Found: C, 73.4; H, 8.98; N, 3.83; O, 4.61; Cl, 9.51.

n) N-(1,1-Dimethylpropyl)-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXIII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXII) of Example 4f) and tert.amylamine. The HCl-salt had m.p. 210° (ethanol-acetone).

$C_{24}H_{36}NO_2Cl$ (406.0) requires: C, 71.00; H, 8.94; N, 3.45; O, 7.88; Cl, 8.73, Found: C, 71.1; H, 9.01; N, 3.60; O, 7.92; Cl, 8.73.

o) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) in 100 ml acetonitrile was treated with tert.butylamine (37 g, 0.5 mol) and the mixture was heated in a pressure bottle at 80° for 4 days. The usual work-up afforded 32 g (100%) crude title compound. The base in ether-acetone was treated with ethereal HCl giving the hydrochloride salt, m.p. 216°–218°.

$C_{20}H_{26}ClNO.HCl$ (368.36) requires: C, 65.21; H, 7.39; N, 3.80; Cl, 19.25, Found: C, 65.1; H, 7.39; N, 3.90; Cl, 18.7.

EXAMPLE 7

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

a) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXV), hydrochloride

A mixture of the secondary amine (LXI) of Example 6l) (29.7 g, 0.1 mol), formic acid (13.8 g, 0.3 mol), and 37% formaldehyde solution (12.5 g, 0.12 mol) was refluxed for 18–24 h. The mixture was then cooled, basified with NaOH, and extracted with ether. The extract was washed with water, dried and evaporated, giving 29.3 g (94%) of a crude oil. The HCl-salt was prepared from ethereal HCl in the usual way, m.p. 199°.

$C_{21}H_{30}NOCl$ (347.9) requires: C, 72.49; H, 8.69; N, 4.03; Cl, 10.19, Found: C, 71.9; H, 8.79; N, 4.23; Cl, 10.1.

b) N-Methyl-N-tert.butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXVI), hydrochloride

The free base was obtained in the same way in 89% yield from the amine (LIII) of Example 6d). The HCl-salt had m.p. 161° (acetone).

$C_{22}H_{32}NOCl$ (362.0) requires: C, 73.00; H, 8.91; N, 3.87; O, 4.42; Cl, 9.08, Found: C, 73.0; H, 8.96; N, 3.94; O, 4.59; Cl, 9.77.

c) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxyphenyl)-propylamine (LXVII), hydrochloride

The free base was obtained in 96% yield from the amine (L) of Example 6a). The HCl-salt had m.p. 187°–190° (acetone-ether).

$C_{22}H_{33}NOCl$ (378.0) requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, , 69.9; H, 8.56; N, 3.53; O, 8.93; Cl, 8.92.

d) N-Methyl-N-tert.butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (LXVIII)

The free base was obtained in 96% yield from the amine (LIV) of Example 6e). M.p. 64° (IPE).

$C_{22}H_{31}NO$ (325.5) requires: C, 81.17; H, 9.60; N, 4.30; O, 4.92, Found: C, 81.0; H, 9.83; N, 4.15; O, 5.03.

e) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXIX)

The free base was obtained in 97% yield from the amine (LV) of Example 6f). M.p. 95° (IPE).

$C_{24}H_{35}NO_2$ (370.0) requires: C, 78.00; H, 9.55; N, 3.79; O, 8.66, Found: C, 78.1; H, 9.57; N, 3.70; O, 8.80.

f) N-Methyl-N-tert.butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)propylamine (LXX), hydrochloride

The free base was obtained in 82% yield from the amine (LX) of Example 6k). The HCl-salt had m.p. 218° (ethanol-acetone).

$C_{21}H_{29}NOClF$ (365.9) requires: C, 68.93; H, 7.99; N, 3.83; Cl, 9.69, Found: C, 69.0; H, 7.97; N, 3.95; Cl, 9.60.

g) N-(1,1-Dimethylpropyl)-N-methyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXXI), hydrochloride

The free base was obtained in 98% yield from the amine (LXII) of Example 6m). The HCl-salt had m.p. 176°–177° (acetone).

$C_{23}H_{34}NOCl$ (376.0) requires: C, 73.47; H, 9.11; N, 3.73; Cl, 9.43, Found: C, 73.4; H, 9.15; N, 3.73; Cl, 9.41.

h) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXXII), hydrochloride

The free base was obtained in 89% yield from the amine (LXIII) of Example 6n). The HCl-salt had m.p. 147° (acetone-ether).

$C_{25}H_{37}NO_2Cl$ (420.1) requires: C, 71.49; H, 9.12; N, 3.34; O, 7.62; Cl, 8.44, Found: C, 70.8; H, 9.20; N, 3.63; O, 7.74; Cl, 8.42.

i) N-Methyl-N-tert.butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (LXXIII)

This compound was obtained as an oil in quantitative yield from the amine (LVIII) of Example 6i).

NMR: 6.5–7.3 (m 8H), 4.3 (t 1H), 3.8 (s 6H), 2.3 (s 3H), 1.0 (s 9H).

j) N-Methyl-N-tert.butyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (LXXIV)

This was obtained as an oil in 95% yield from the amine (LVI) of Example 6g).

k) N-Methyl-N-tert.butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propylamine (LXXV), hydrochloride

The free base was obtained in 92% yield from the amine (LVII) of Example 6k). The HCl-salt had m.p. 170°–171° (acetone-ether).

$C_{36}H_{44}NO_2Cl$ (558.2) requires: C, 77.46; H, 7.95; N, 2.51; O, 5.73; Cl, 6.35, Found: C, 77.6; H, 7.86; N, 2.42; O, 5.89; Cl, 6.31.

l) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dimethoxyphenyl)propylamine (LXXVI), hydrochloride

The free base was obtained in 96% yield from the amine (LIX) of Example 6j). The HCl-salt had m.p. 180°–190° and seems to be associated with ¼ mol of water.

$C_{24}H_{36}NO_4Cl$ ¼ H_2O (447.0) requires: C, 64.48; H, 8.34; N, 3.13; O, 16.11; Cl, 7.93, Found: C, 64.5; H, 8.27; N, 3.02; O, 16.2; Cl, 8.19.

m) N-Methyl-N-tert.butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (LXXVII)

This was obtained as an oil in 98% yield from the amine (LI) of Example 6b).

NMR: δ 6.9–7.3 (m 18H), 2.1 (s 3H), 1.0 (s 9H).

n) N-Methyl-N-tert.butyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine (LXXVIII)

This was obtained as an oil in 97% yield from the amine (LII) of Example 6c).

NMR: 6.9–7.3 (m 14H), 5.0 (s 4H), 4.5 (t 1H), 2.2 (s, 3H), 0.9 (s, 9H).

o) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The secondary amine from Example 6o) (25.3 g, 0.076 mol) was refluxed for 18 h with formic acid (9.2 g, 0.2 mol) and 35% formaldehyde solution (8.5 g, 0.1 mol). Work-up gave 25.6 g, (97.5%) crude base. This was dissolved in acetone and treated with an equimolar quantity of oxalic acid in acetone giving beige crystals of the title compound, hydrogen oxalate, m.p. 165°.

$C_{21}H_{28}ClNO.C_2H_2O_4$ (436.0) requires: C, 63.37; H, 6.94; N, 3.21; Cl, 8.13 , Found: C, 62.7; H, 6.83; N, 3.10; Cl, 7.97.

p) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5p). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ad).

q) N-1-Adamantyl-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5q). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ae) without further purification.

EXAMPLE 8

Preparation from olefinic precursors

a) N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-hydroxy-3-phenylpropylamine (LXXIX)

A solution of diisopropylamine (10.1 g, 0.1 mol) in dry ether (100 ml) was cooled to −10°. A solution of butyl lithium in hexane (65 ml, 0.1 mol) was added, and the mixture was stirred at −10° for 20 min. A solution of N-ethylidene-tert.butylamine (10 g, 0.1 mol) in dry ether (100 ml) was added and the solution was stirred at 0° for 20 min. After cooling to −30° a solution of 2,6-dimethoxybenzophenone (24.1 g, 0.1 mol) in dry ether (100 ml), containing 30 ml THF, was added. The mixture was then stirred at ambient temperature for 20 h and hydrolized with water. The organic phase was washed with water, dried and evaporated, giving 32 g (94%) of N-(3-(2,6-dimethoxyphenyl)-3-hydroxy-3phenylpropylidene)tert.butylamine as an oil.

This oil was dissolved in absolute ethanol (250 ml), the solution was cooled to −5°, and $NaBH_4$ (5.7 g, 0.15 mol) was added portionwise. The mixture was stirred at 0° for ½ h, then at ambient temperature for 3 h. Most of the solvent was distilled off in vacuum, the residue was treated with water, extracted with ether, washed with water, and extracted with 2N HCl. The extract was washed with ether, basified with NaOH, extracted with ether, dried and evaporated, giving 30 g of the title amine.

The HCl-salt had m.p. 203°–204° (acetone-ether) and seems to be associated with ½ mol of water.

$C_{21}H_{29}NO_3.HCl.½\ H_2O$ (384.5) requires: C, 65.60; H, 8.01; N, 3.64; O, 13.52, Found: C, 65.9; H, 8.11; N, 3.64; O, 13.7.

b) N-tert.Butyl-3-(2,6-dimethoxyphenyl)-3-phenyl-2-propene-1-amine (LXXX)

The above amine from step a) (21 g, 0.061 mol) was added to 6.3N H_2SO_4 (20 ml, 0.126 mol). The mixture was stirred on a boiling water bath for 2 h, cooled, basified, and extracted with ether. The extract was washed, dried and evaporated, giving 17.8 g, (90%) of the title olefin as a clear oil. The HCl-salt had m.p. 220°–22°, and was associated with ¼ mol of water.

$C_{21}H_{27}NO_2.HCl.¼\ H_2O$ requires: C, 68.82; H, 7.86; N, 3.82; O, 9.82; Cl, 9.68, Found: C, 68.8; H, 7.89; N, 3.92; O, 9.81; Cl, 9.44.

c) N-Methyl-N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropylamine (LXXXI), hydrogen fumarate hydrogen fumarate

The olefinic amine from step b) (16.3 g, 0.05 mol) in methanol (250 ml) containing 0.5 g of a 10% Pd/C catalyst, was hydrogenated at ambient temperature and pressure. The mixture was then filtered through Celaton, the filtrate was taken to dryness, giving 16.3 g (100%) of N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropylamine. The HCl-salt had m.p. 244° (ethanol).

$C_{21}H_{29}NO_2.HCl$ (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.3; H, 8.29; N, 3.83; O, 9.27; Cl, 9.75.

The above secondary amine, as the free base, was methylated with formaldehydeformic acid as described in Example 7, giving the tertiary amine in 96% yield. The fumaric acid salt had m.p. 185°–190° (acetone).

$C_{26}H_{35}NO_6$ (457.6) requires: C, 68.25; H, 7.71; N, 3.06; O, 20.95, Found: C, 67.8; H, 7.59; N, 3.05; O, 21.6.

EXAMPLE 9

Removal of O-protective groups

a) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (LXXXII), hydrochloride

The amine (XLIX) of Example 5k) (20.8 g, 0.064 mol) in methylene chloride (150 ml) was cooled below 0°. A 1N solution of BBr_3 in CH_2Cl_2 (64 ml, 0.064 mol) was then added dropwise, the solution was then kept in the cooler (5°) for 2–5 days, and volatile material was distilled off at <50°. The residual syrup was basified, extracted with ether, the extract was washed with water, dried and evaporated, giving a viscous syrup. The HCl-salt had m.p. 222° (methanol-ether), yield 31%.

$C_{21}H_{29}NO.HCl$ (347.9) requires: C, 72.49; H, 8.69; N, 4.03; O, 4.60; Cl, 10.19, Found: C, 72.0; H, 8.72; N, 3.74; O, 5.06; Cl, 10.3.

The following compounds were obtained in the same way.

b) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine (LXXXIII), hydrogen fumarate

From the amine (LXIV) of Example 5l). Crude yield 78%. M.p. fumaric acid salt=indefinite.

$C_{28}H_{37}O_5$ (467.6) requires: C, 71.9; H, 7.91; N, 3.00; O, 17.1, Found: C, 71.8; H, 8.41; N, 3.01; O, 16.6.

c) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (LXXXIV), hydrochloride

From the amine (XL) of Example 5c). Crude yield 85%. HCl-salt, m.p. 209°–210° (acetone-ether).

$C_{22}H_{31}NO.HCl.¼\ H_2O$ (366.5) requires: C, 72.09; H, 8.95; N, 3.82; O, 5.46; Cl, 9.67, Found: C, 72.3; H, 8.95; N, 3.71; O, 5.68; Cl, 9.61.

d) N-Methyl-N-tert.butyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (LXXXV), hydrochloride

From the amine (LXVI) of Example 7b). Crude yield 100%. HCl-salt, m.p. >260° (ethanol).

$C_{21}H_{29}NO.HCl$ (347.4) requires: C, 72.49; H, 8.69; N, 4.03; Cl, 10.19, Found: C, 72.7; H, 8.58; N, 3.81; Cl, 10.95.

e) N,N-Diisopropyl-3,3-bis-(2-hydroxyphenyl)-propylamine (LXXXVI), hydrochloride

From the amine (XXXVIII) of Example 5a). Crude yield 57%. HCl-salt, m.p. 257° (ethanol-ether).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.3; H, 8.37; N, 3.95; O, 9.23; Cl, 9.40.

f) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)-propylamine (LXXXVII), hydrochloride

From the amine (LXVII) of Example 7c). Crude yield 100%, m.p. 190°. HCl-salt, m.p. 252° (ethanol).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C, 68.65; H, 8.06; N, 4.00; Cl, 10.13, Found: C, 68.4; H, 8.06; N, 4.17; Cl, 9.59.

g) N,N-Diisopropyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (LXXXVIII), hydrochloride

From the amine (XLI) of Example 5d). Crude yield 90%. HCl-salt, m.p. 217° (ethanol).

$C_{22}H_{31}NO$.HCl.$\frac{1}{4}$ H_2O (366.5) requires: C, 72.09; H, 8.96; N, 3.82; O, 5.46; Cl, 9.67, Found: C, 72.3; H, 8.91; N, 3.93; O, 5.27; Cl, 9.46.

h) N,N-Diisopropyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (LXXXIX), hydrochloride

From the amine (XLII) of Example 5e). Crude yield 93%, m.p. 166°. HCl-salt, m.p. 220° (ethanol).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C, 70.47; H, 8.74; N, 3.57; Cl, 9.05, Found: C, 70.6; H, 8.78; N, 3.71; Cl, 8.93.

i) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (XC), hydrochloride

From the amine (LXIX) of Example 7e). Crude yield 79%, m.p. 199°–201° (IPE). HCl-salt, m.p. 220° (acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, 69.9; H, 8.70; N, 3.75; O, 8.81; Cl, 9.15.

j) N-Methyl-N-tert.butyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (XCI), hydrochloride

From the amine (LXVIII) of Example 7d). Crude yield 100%. HCl-salt, m.p. 240° (ethanol).

$C_{21}H_{29}NO$.HCl (347.9) requires: C, 72.49; H, 8.69; N, 4.03; O, 4.60; Cl, 10.19, Found: C, 72.5l H, 8.75; N, 4.06; O, 4.90; Cl, 10.1.

k) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-hydroxyphenyl)propylamine (XCII), hydrochloride

From the amine (XLVII) of Example 5j). Crude yield 72%. HCl-salt, m.p. 183° (acetone-ethanol).

$C_{21}H_{27}FNO$.HCl (364.9) requires: C, 69.12; H, 7.73; N, 3.83, Found: C, 69.1; H, 8.09; N, 3.82.

l) N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCIII), hydrochloride

From the amine (XLV) of Example 5h). Crude yield 31%. HCl-salt, m.p. 205°–210° (ethanol-acetone-ether).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.5; H, 8.33; N, 3.72; O, 8.91; Cl, 9.87.

m) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (XCIV), hydrochloride

From the amine (LXXII) of Example 7h). Crude yield 100%, m.p. 190°–195°. HCl-salt, m.p. 235°–240° (ethanol-acetone-ether).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C, 70.47; H, 8.74; N, 3.57; O, 8.16; Cl, 9.05, Found: C, 70.0; H, 8.96; N, 3.54; O, 8.11; Cl, 9.19.

n) N-Methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCV), hydrobromide

From the amine (LXXIII) of Example 7i). Crude yield 78%, m.p. 260°. HBr-salt, m.p. >260° (ethanol).

$C_{20}H_{25}NO_2$.HBr (394.4) requires: C, 60.9; H, 7.16; N, 3.55; O, 8.11; Br, 20.27, Found: C, 60.8; H, 7.18; N, 3.29; O, 8.38; Br, 20.2.

o) N,N-Diisopropyl-3,3-bis-(2,4-dihydroxyphenyl)-propylamine (XCVI), hydrochloride

From the amine (XLVI) of Example 5i). The HCl-salt, consisting of an amorphous brown powder, did not give a satisfactory elemental analysis because of incomplete combustion.

p) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dihydroxyphenyl)propylamine (XCVII), hydrochloride

From the amine (LXXVI) of Example 7l). Crude yield 87%, m.p. 260°. The HCl-salt did not give a satisfactory elemental analysis because of incomplete combustion.

q) N,N-Diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCVIII), hydrochloride

The amine (XLIII) of Example 5f) in the form of the free base (32 g, 0.063 mol) in methanol (500 ml) containing 5 g of a 5% Pd/C catalyst was hydrogenated at ambient temperature and pressure. After 2 h the reaction was complete. The mixture was filtered, the filtrate was taken to dryness, the residue was dissolved in acetone and treated with ethereal HCl, giving 19.8 g (87%) of a crude salt, m.p. 260°. Recrystallization from methanol gave white crystals, m.p. 260°.

$C_{21}H_{29}NO_2$.HCl $\frac{1}{4}$ H_2O (368.6) requires: C, 68.44; H, 8.36; N, 3.80; O, 9.77; Cl, 9.62, Found: C, 68.4; H, 8.40; N, 3.60; O, 10.3; Cl, 9.42.

The following compounds were prepared in the same way.

r) N-Methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCIX), hydrochloride

From the amine (LXXIV) of Example 7j). Crude yield 90%. HCl-salt, m.p. >270° (methanol-water).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C, 68.65; H, 8.06; N, 4.00; O, 9.14; Cl, 10.13, Found: C, 68.9; H, 8.02; N, 3.93; O, 9.60; Cl, 10.5.

s) N,N-Diisopropyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (C), hydrochloride

From the amine (XLIV) of Example 5g). Crude yield 100%. HCl-salt, m.p. 253° (methanol-ether).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C, 70.47; H, 8.74; N, 3.57; O, 8.16; Cl, 9.05, Found: C, 70.5; H, 8.74; N, 3.55; O, 8.47; Cl, 8.03.

t) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (CI), hydrochloride

From the amine (LXXV) of Example 7k). Crude yield 97%, a yellow powder.HCl-salt, m.p. 260° (methanol-acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, 69.9; H, 8.68; N, 3.67; O, 8.85; Cl, 9.24.

u) N,N-Diisopropyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CII), hydrochloride

From the amine (XXXIX) of Example 5b). Crude yield 100%. HCl-salt, m.p. 174°–176° (acetone).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.5; H, 8.33; N, 3.66; O, 9.37; Cl, 9.63.

w) N-Methyl-N-tert.butyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CIII), hydrochloride

From the amine (LXXVII) of Example 7m). Crude yield 100%, a white powder.HCl-salt, m.p. 209°–210°, slow heating, (methanol-acetone).

$C_{20}H_{27}NO_2.HCl.\frac{1}{4}H_2O$ (358.9) requires: C, 66.92; H, 8.14; N, 3.90; O, 11.14; Cl, 9.88, Found: C, 66.9; H, 8.12; N, 3.76; O, 11.8; Cl, 9.74.

x) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (CIV), hydrochloride

From the amine (LXXVIII) of Example 7n). Crude yield 100%. HCl-salt, m.p. 255° (acetone-ether).

$C_{20}H_{27}NO.HCl$ (333.9) requires: C, 71.94; H, 8.45; N, 4.20; Cl, 10.62, Found: C, 71.9; H, 8.43; N, 4.01; Cl, 10.5.

y) N-Methyl-N-tert.butyl-3-(2,6-dihydroxyphenyl)-3-phenylpropylamine (CV), hydrochloride

From the amine (LXXXI) of Example 8c) with BBr_3, in low yield. HCl-salt, m.p. 170° (ethanol-ether).

$C_{20}H_{27}NO_2.HCl.\frac{1}{2}H_2O$ (358.9) requires: C, 66.93; H, 8.14; N, 3.40; O, 11.14; Cl, 9.87, Found: C, 67.4; H, 8.28; N, 3.63; O, 10.9; Cl, 9.99.

z) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The base from Example 5m) (11.7 g, 0.032 mol) was treated with pyridine (7.6 g, 0.096 mol) and conc. HCl (13 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205°–215° for 1½ h. The melt was cooled somewhat, water was added, the mixture was digested in a boiling water bath and cooled. 2N HCl was added, the salt was filtered off, washed with 2N HCl and dried, giving 11.0 g (90%) white salt m.p. 200° . Recrystallization from acetone gave the hydrochloride of the title compound, m.p. 202°–203°.

$C_{21}H_{28}ClNO.HCl$ (382.4) requires: C, 65.96; H, 7.64; N, 3.66; Cl, 18.54, Found: C, 66.0; H, 7.88; N, 3.63; Cl, 18.3.

aa) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The free base from Example 7o) (10.5 g, 0.03 mol) was treated with pyridine (7.0 g, 0.09 mol) and conc. HCl (12 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205°–215° for 1½ h. The melt was cooled somewhat, excess of 2N NaOH was added, the mixture was extracted with ether, the extract was washed with water, dried and evaporated giving 7.5 g (88%) crude syrup. This was dissolved in ether and treated with ethereal HCl giving 8 g (83%) of hydrochloride salt. Recrystallization from acetone-2N HCl gave the hydrochloride of the title compound, m.p. 260°.

$C_{20}H_{26}ClNO.HCl$ (368.4) requires: C, 65.21; H, 7.39; N, 3.80; Cl, 19.25, Found: C, 65.0; H, 7.30; N, 3.73; Cl, 18.9.

ab) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-2,2,5,5-tetramethylpyrrolidine

The crude amine from Example 5n) was hydrogenolysed as described in Example 9q). The free amine was obtained as an oil which was converted to the hydrochloride and crystallized from 2-propanol. M.p. 250° C.

$C_{23}H_{31}NO.HCl$ (374.0) requires: C, 73.86; H, 8.63; N, 3.75; O, 4.28; Cl, 9.48, Found: C, 73.8; H, 8.71; N, 3.59; O, 4.80; Cl, 9.45.

ac) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-4-hydroxy-2,2,6,6-tetramethylpiperidine

The benzyloxy compound from Example 5o) was hydrogenolysed as described in Example 9q). The free base was converted to the hydrochloride semihydrate which was crystallized from acetone. The compound melts with decomposition at about 150° C.

$C_{24}H_{33}NO_2.HCl.\frac{1}{2}H_2O$ (413.0) requires: C, 69.79; H, 8.54; N, 3.39; O, 9.68; Cl, 8.58, Found: C, 70.0; H, 8.67; N, 3.47; O, 9.98; Cl, 8.13.

ad) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7p) was hydrogenolysed as described in Example 9q). The amine, obtained as a glassy mass, was converted to the hydrochloride which was obtained as an amorphous solid on precipitation from ethanol with ether.

$C_{20}H_{27}NO_2.HCl$ (349.9) requires: C, 68.65; H, 8.06; N, 4.00; O, 9.15; Cl, 10.13, Found: C, 68.25; H, 8.18; N, 3.98; O, 9.12; Cl, 10.0.

ae) N-1-Adamantyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7q) was hydrogenolysed as described in Example 9q). The free hydroxyamine was obtained as a glassy mass. It was dissolved in anhydrous ether and treated with an excess of hydrogen chloride in ether. The hydrochloride precipitated as a powder which decomposed at about 220° C.

$C_{26}H_{33}NO.HCl$ (412.0) requires: C, 75.79; H, 8.32; N, 3.40; O, 3.88; Cl, 8.61, Found: C, 75.3; H, 8.01; N, 3.22; O, 3.45; Cl, 8.96.

EXAMPLE 10

Reduction of amides

a) N,N-Diisopropyl-3- (2-methoxy-5-methylphenyl)-3-phenylpropylamine

3-(2-Methoxy-5-methylphenyl)-3-phenylpropionic acid (12.8 g, 0.05 mol) (J. D. Simpson & H. Stehphen, J. Chem. Soc. 1956 1382) and thionyl chloride (50 ml) are heated on a water bath for 3 h. The excess of thionyl chloride is distilled off under reduced pressure. The remaining crude 3-(2-methoxy-5-methylphenyl)3-phenylpropionyl chloride is dissolved in 50 ml of dichloromethane and added dropwise to a stirred solution of diisopropylamine (20.2 g, 0.20 mol) in 200 ml of dichloromethane at about 0° C. The solution is left for 2 h, the solvent is distilled off and the remaining material is treated with water. The solid product consisting of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropionamide is filtered off, dried and added in small portions to a stirred suspension of lithium aluminium hydride (6.0 g, 0.16 mol) in dry ether (700 ml). The mixture is refluxed for 2 days. Excess of hydride is destroyed by the careful addition of water, the ether layer is separated and dried with anhydrous sodium sulfate. After filtration the solution is added to a solution of excess fumaric acid in ether. The precipitated salt is collected and crystallized from 2-propanol. The hydrogen fumarate melts at 176° C.

b) N-Methyl-N-tert.butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine was similarly prepared. The hydrochloride melts at 161° C.

EXAMPLE 11

a) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

A solution of chlorine (7,1 g, 0,10 mol) in acetic acid (500 ml) is added dropwise to a stirred solution of N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3 -phenylpropylamine (29.7 g. 0.10 mol) in acetic acid (200 ml) with stirring. After 2 h the solvent is distilled off under reduced pressure and the crude hydrochloride left is recrystallized from 2-propanol. Melting point 260° C.

b) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared. The hydrochloride melts at 202°–3° C.

EXAMPLE 12

Separation of(+)- and (−)-enantiomers

(±)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (31.1 g, 0.10 mol) is dissolved in 300 ml of ethanol. A solution of L(+)-tartaric acid (15.0 g, 0.10 mol) in 400 ml of ethanol is added. The mixture is heated a few minutes in a boiling water bath and seeded with crystals obtained by cooling and scratching a small sample of the main solution. The mixture is chilled at about 4° C. over-night whereupon the crystalline precipitate is filtered off, washed with cold ethanol and recrystallized repeatedly from ethanol. The pure (−)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine hydrogen L-(+)-tartrate thus obtained has $[\alpha]_D^{20}$ −10.6° (c=5% in methanol). The free amine is obtained by alkalisation of an aqueous solution, extraction into ether, drying and evaporation of the solvent. Sticky oil, $[\alpha]_D^{20}$ −5.4° (c=5% in methanol).

(+)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared using D-(−)-tartaric acid. The hydrogen-D-(−)tartrate has $[\alpha]_D^{20}$ +10.0° . The free amine has $[\alpha]_D^{20}$ +5.6° , both measured as 5% solutions in methanol.

EXAMPLE 13 (CONTINUATION OF EXAMPLE 1)

Preparation of 4-phenyl-3,4-dihydrocoumarins

g) 4-(2-Methoxyphenyl)6-methyl-3,4-dihydrocoumarin (CIV)

A mixture of 2-methoxycinnamic acid (178 g, 1.0 mol), p-cresol (108 g, 1.0 mol), and p-touenesulphonic acid monohydrate (47.5 g, 0.25 mol) was stirred on a boiling water-bath for about 2 h during which time the system was evacuated with a waterpump to remove formed water. The solid was then broken up and washed copiously with water. The granular material was then stirred with a large volume of saturated $NaHCO_3$ solution containing some 10% acetone. The product was filtered off, washed dried and recrystallised from acetone affording 167 g (62,5%) white crystals of the desired lactone, m.p. 140°.

$C_{17}H_{16}O_3$ (268.3) requires: C, 76.10; H, 6.01; O, 17.89, Found: C, 76.0; H, 5.97; O, 17.9.

h) 6-Chloro-4-(2-methoxyphenyl)-3,4-dihydrocoumarin (CVII) was prepared in a similar way in 49% yield from 2-methoxycinnamic acid and p-chlorophenol, the reaction temperature being 130° in this case. M.p. 172°–173° (acetone).

$C_{16}H_{13}O_3$ (288.7) requires: C, 66.56; H, 4.54; O, 16.62, Found: C, 66.8; H, 4.45; O, 16.5.

EXAMPLE 14 (CONTINUATION OF EXAMPLE 2)

Preparation of 3,3-diphenylpropionic acid esters

l) Methyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propionate (CVIII) was obtained as an oil in 75% yield from the lactone CVI of Example 13g in the manner described for the ester VI of Example 2a).

m) Methyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propionate (CIX) was obtained as an oil in the same way in 97% yield from the lactone CVII of Example 13.

EXAMPLE 15 (CONTINUATION OF EXAMPLE 3)

Preparation of 3,3-diphenylpropanols

m) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propanol (CX) was obtained in 84% yield from the ester CIX of Example 14m in the manner described for the propanol XVI of Example 3a), except that the reduction was carried out in toluene with a 10% molar excess of a 3.4M toluenic solution of sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH) instead of $LiAlH_4$. M.p. 70°–72°(IPE).

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propanol (CXI) was obtained in the same way in quantitive yield from the ester CVIII of Example 141). The product consisted of a golden oil of 89% purity according to GC.

EXAMPLE 16 (CONTINUATION OF EXAMPLE 4)

Preparation of 3,3-diphenylpropyl-p-toluenesulphonates

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propyl-p-toluene-sulphonate (CXII) was prepared in the same way as the tosylate XXVII of Example 4a) in quantitative yield from the propanol CXI of Example 15n) using CH_2Cl_2 as solvent instead of chloroform. M.p. 101° (ether/IPE).

$C_{25}H_{28}O_5S$ (440.57) requires: C, 68.16; H, 6.41; S, 7.28, Found: C, 68.3; H, 6.51; S, 7.20.

o) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propyl-p-toluenesulphonate (CXIII) was obtained in the same way in quantitative yield from the propanol CX of Example 15m. M.p. 97°–98° (acetone-/IPE).

$C_{24}H_{25}ClO_5S$ (460.92) requires: C, 62.54; H, 5.47; S, 6.94; Cl, 7.69, Found: C, 63.0; H, 5.65; S, 6.95; Cl, 7.70.

EXAMPLE 17 (CONTINUATION OF EXAMPLE 5)

Preparation of tertiary 3,3-diphenylpropylamines

r) N,N-Diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXIV) was obtained as an oil in 94% yield from the tosylate CXIII of Example 16o) in the manner described for the amine XXXVIII of Example 5a). Purity by GC=99.9%.

s) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXV) was obtained in the same way in 49% crude yield from the tosylate CXV of Example 16n). After chromatographic purification on an Si-gel 60 column (eluation with light petroleum), the product (oil) had a purity of 100% according to GC.

t) N-[(2-Benzyloxy-5-methyl)-3-phenyl]-2,2,5,5-tetramethylpyrrolidine (CXVI) was prepared from 3-(2-benzyloxy-5-methyl)-3-phenylpropyl tosylate and 2,2,5,5-tetramethylpyrrolidine following the directions given in Example 5a). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 20aj).

EXAMPLE 18 (CONTINUATION OF EXAMPLE 6)

Preparation of secondary 3,3-diphenylpropylamines

p) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXVII) was prepared in

quantitative yield from the tosylate CXIII of Example 16o) in the manner described for the amine L of Example 6a). The HCl-salt had m.p. >260°.

$C_{21}H_{28}ClNO_2$.HCl (398.38) requires: C, 63.3; H, 7.34; N, 3.52; Cl, 17.80, Found: C, 63.2; H, 7.46; N, 3.49; Cl, 17.4.

q) N-tert.Butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXVIII) was obtained in a similar way in 89% crude yield from the tosylate CXII of Example 16n). The HCl-salt had m.p. 225°.

$C_{22}H_{31}O_2N$.HCl (377.97)

Requires: C, 69.91; H, 8.54; N, 3.71; Cl, 9.38; O, 8.47, Found: C, 69.8; H, 8.73; N, 3.60; Cl, 9.45; O, 8.79.

EXAMPLE 19 (CONTINUATION OF EXAMPLE 7)

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

r) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXIX) was prepared in 89% yield from the amine CXVII of Example 18p) in the manner described for the amine LXI of Example 7a). The HCl-salt was prepared by treating an acetonic solution of the free base with conctrated hydrochloric acid. M.p. 130°.

$C_{22}H_{30}ClO_2N$.HCl.H_2O (430.42)

Requires: C, 61.39; H, 7.74; N, 3.25; Cl, 16.47, Found: C, 62.0; H, 7.93; N, 3.26; Cl, 16.5.

s) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXX) was prepared in a similar way in 98% yield from the amine CXVIII of Example 18q). The free base (oil) had a purity of 96% by GC.

EXAMPLE 20 (CONTINUATION OF EXAMPLE 9)

Removal of O-proptective groups

af) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methylphenyl)propylamine (CXXI)

The amine CXV from Example 17s) (26.5 g, 0.072 mol) in methanol was treated with a slight excess of concentrated hydrochloric acid. The mixture was taken to dryness in vacuum, pyridinium chloride (25.4 g, 0.22 mol) was added and the mixture was then heated at 200°–205° for 1½ h. The mixture was cooled to about 80°, acetone (20 g) was added followed by addition of little water. The salt was filtered off, washed with diluted HCl and dried. Recrystallisation from absolute ethanol/ether gave 17.5 g (64.3%) of a white salt, m.p. >250°. Purity by GC=100%.

$C_{22}H_{31}NO_2$.HCl (377.97) Requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, 69.8; H, 8.65; N, 3.57; O, 8.76; Cl, 9.51.

ag) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)propylamine (CXXII was prepared in the same way in 37% yield from the amine CXIV of Example 17r). The HCl-salt had m.p. 214° (ethanol).

$C_{21}H_{28}NO_2$.HCl (398.38) Requires: C, 63.31; H, 7.34; N, 3.52; O 8.03; Cl, 17.80, Found: C, 63.1; H, 7.34; N, 3.40; O, 8.15; Cl, 17.8.

ah) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methylphenyl)propylamine (CXXIII) was prepared in the same way in 30% yield from the amino CXX of Example 19s). The HCl-salt had m.p. 240° (acetone).

$C_{21}H_{29}NO_2$.HCl (363.94) requires: C, 69.3; H, 8.31; N, 3.58; Cl, 9.74, Found: C, 69.0; H, 8.35; N, 3.65; Cl, 9.76.

ai) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)propylamine (CXXIV) was prepared in the same way in 24% yield from the amine CXIX of Example 19r). M.p. >250°.

$C_{20}H_{26}ClNO_2$.HCl (384.36) requires: C, 62.50; H, 7.08; N, 3.65; Cl, 18.45, Found: C, 62.5; H, 7.09; N, 3.63; Cl, 18.4.

aj) N-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-2,2,5,5-tetramethylpyrrolidine (CXXV) was obtained when the O-benzylated amine CXVI of Example 17t) was hydrogenolyzed as described in Example 9q. The hydrochloride melts at 240°.

$C_{24}H_{34}ClNO$ (388.0) requires: C, 74.29; H, 8.83; N, 3.61; Cl, 19.14, Found: C, 73.9; H, 8.90; N, 3.52; Cl, 9.48.

EXAMPLE 21 (CONTINUATION OF EXAMPLE 10)

Reduction of amides

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamine

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamide was obtained as o pale yellow oil in quantitative yield from 3-(2-methoxyphenyl)-3-phenylpropionic acid in the manner described for the amide of Example 10a). This amide (27 g, 0.08 mol) in toluene (50 g) was added dropwise under r.t. to a 3.4M toluenic solution of SMEAH (50 g, 0,17 mol) diluted with an equal weight of toluene. The mixture was stirred at 60°–70° for 2 h, cooled, treated with excess od 2N NaOH. The organic phase was separated, washed with water and extracted with 2N HCl. The acidic extract was washed with ether, basified, extracted with ether, dried and evaporated giving 17.1 g (66%) free base. This was dissolved in acetone (75 ml) and treated with 6.6 g fumaric acid dissolved in methanol, affording 20 g of the fumaric acid salt, m.p. 163°–164°.

$C_{22}H_{31}ON.C_4H_4O_4$ (441.58) requires: C, 70.72; H, 7.99; N, 3.17; O, 18.12, Found: C, 70.7; H, 7.96; N, 3.13; O, 18.0.

EXAMPLE 22

Separation of (+)- and (−)-enantiomers

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen tartrate

The racemic amine (LXXXVIII of Example 9g) (48.8 g, 0.15 mol) was dissolved in 500 ml of 95% ethanol and mixed with a solution of L(+)-tartaric acid (22.5 g, 0.15 mol) in 500 ml of ethanol. The mixture was left over night at +4°. The precipitated salt was collected by filtration and washed with ethanol and ether. The yield of crude salt with $[\alpha]_{546}^{25}$ +29.5° (C 5%, methanol) was 34,3 g. Two recrystallisations from ethanol afforded 21.8 g with $[\alpha]_{546}^{25}$ +36.0°.

$C_{26}H_{37}NO_7$ requires: C, 65.66; H, 7.84; N, 2.95; O, 23.55, Found: C, 65.9; H, 8.06; N, 2.90; O, 23.5.

(−)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen D(−)-tartrate was similarly prepared using D(−)-tartaric acid.

$[\alpha]_{546}^{25}$ −35.8°.

Found: C, 65.6; H, 8.00; N, 2.83; O, 23.6.

Several of the compounds according to the invention were tested with regard to anti-cholinergic, anti-noradrenaline, and anti-calcium effects, toxicity and effect

on the heart rate. The test procedures are described below, and the test results are reported in Table 1. For comparison purposes the testing also included the commercially available drug terodiline and a structurally similar compound, N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, disclosed as an antidepressant in U.S. Pat. No. 3,446,901, GB-A-1.169.944, and GB-A-1.169.945. The test results clearly show that the compounds according to the invention are superior to the known compounds especially as regards selectively between the desired anti-cholinergic activity and the undesired side-effects.

a) Anticholinergic activity on isolated urinary bladder

Male guinea-pigs, weighing 250–350 g, were killed by a blow on the head and exsanguinated. The urinary bladders were quickly removed and placed in Na+-Krebs, in which they were kept throughout the dissection procedure. The bladders were dissected free from adherent fat and connective tissue before they were cut open by an incision on each side from the base towards apex. The mucosa was carefully removed with a pair of scissors. Four strips, approximately 3–5 mm long were prepared by cutting in a parallel direction to the longitudinal muscle fibers, on each half of the bladder.

The bladder strips were immediately mounted vertically in 5 ml organ baths containing Na+-Krebs solution aerated with carbogene gas to maintain the pH at about 7.4. The temperature, 37° C., was thermostatically controlled by a Lauda MS3 thermostatic circulator. The preparations were suspended between two hooks, one of which was connected to a Grass Instruments FTO3 force transducer. The isomeric tension of the preparations was recorded by a Grass polygraph model 79D. The resting tension was applied to approximately 5 mN. The strips were allowed to stabilize for at least 45 minutes. During this period the resting tension was adjusted to 5 mN and the preparations were repeatedly washed.

In the preliminary experiments concentration-effect curves for carbachol (carbamylcholin chloride) were studied, in order to determine a suitable agonist concentration for inhibition studies with antagonist. The carbachol concentration chosen, 3×10^{-6}M, produced a submaximal contractant response (70%). In the inhibition studies, the strips were contracted with carbachol (3×10^{-6}M) every 15 minutes. The strips were washed three times after every agonist addition. This procedure was repeated until a reproducible contractant response was observed. A variation of about 10% for three subsequent contractions was accepted as reproducible.

Initially each antagonist was tested in a concentration of 10^{-6}M, on two bladder-strips from different guinea-pigs. When a reproducible response with 3×10^{-6}M carbachol was obtained, the strips were incubated with the antagonist for 15 minutes before the next carbachol was added. If the antagonist produced more than 50% inhibition of the response to carbachol, a complete concentration-inhibition curve was also made. In the complete inhibition curves, the strips were then incubated for 60 minutes with a fixed concentration of the antagonist before the next addition of carbachol. The effect of the antagonists was calculated as per cent inhibition of the mean of the initial agonist-induced contractions. To generate concentration-inhibition curves the antagonists were studied in 6–8 concentrations and for each concentration a fresh preparation was used, i.e. the strips were only exposed to the antagonist once before they were discarded.

b) Antagonistic effect to noradrenaline and calcium on the portal vein Preparation of isolated portal vein from rat

Animals: Albino, male rats, weighing about 200 g.
Bath volume: 5 ml
Buffer: Na+-Krebs, modified by K. E. Andersson
Temperature: 37° C.
Gas: Carbogene (93.5% O_2+6.5% CO_2)
Muscle tension: 0.5 g

The rat is killed by a blow on the neck and decapitated. The abdomen is opened, the vein is dissected free from fat, cut open longitudinally and mounted in an organ bath. Changes in isometric tension is registered by a force displacement transducer, connected to an amplifier and a writing oscillograph.

Noradrenaline-antagonism on portal vein

Doses: Noradrenaline 3×10^{-7}M

The chosen doses give about 70% of maximal response. The agonist is added to the bath at 10-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 10 minutes noradrenaline is added. The next concentration of the test substance is added when the original response of the agonist is obtained.

The antagonistic effect of the substance is calculated as per cent inhibition of the mean response by three preceding doses of the agonist.

Ca-antagonistic effect on portal vein

10 mM K+-solution is added to the Krebs buffer to stabilize the spontaneous myogenic activity of the vein. The amplitude of the muscle contractions is measured. The test substance is added to the bath in cumulative doses until total inhibition is obtained.

c) Histamine-antagonism on isolated ileum

Preparation of isolated ileum from guinea pigs

Animals: Guinea pigs of both sexes, weighing about 350 g.
Bath volume: 5 ml
Buffer: Na+-Krebs, modified by K. E. Andersson
Temperature: 37° C.
Gas: Carbogene (93.5% O_2+6.5% CO_2)
Muscle tension: 0.5 g

The guinea pig is killed by a blow on the neck and decapitated. The abdomen is opened and about 2 cm of the ileum is cut off about 15 cm above the ileocaecal junction. The piece of ileum is washed with buffer and mounted in an organ bath. Changes in isometric tension is recorded by a force displacement transducer, connected to an amplifier and a writing oscillograph.

Dose: 5×10^{-7}M of histamine.

The chosen dose of histamine gives about 70% of maximal response. The agonist is added to the bath at 3-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 2–10 minutes a new contraction is induced by histamine. The next concentration of the test substance is added when the original response of the agonist is obtained.

The agonistic effect of the test substance is calculated as per cent inhibition of the mean response by three preceding doses of histamine.

d) Acute toxicity in mice

The antagonists to be tested were dissolved in 0.9% NaCl. If they were not soluble in 0.9% NaCl they were dissolved in double distilled water. The solutions were prepared on the day of the experiment.

Procedure

White male mice, 25 g, were placed in a mouse holder. The tested compounds were given as i.v. bolus doses in one of the four tail-veins, with a volume of 0.01 ml/g mouse. Each substance concentration was given to a group of four mice. 4-5 different concentrations of the antagonists were made and tested.

The acute lethal dose (LD_{11}) was the lowest concentration of the anticholinergic drug where 4 mice of 4 tested died within 5 minutes after an i.v. bolus dose.

LD_{50}-interval: The LD_{50}-interval was between the highest dose where 4 mice survived and the lowest dose where 4 mice died within 5 minutes after an i.v. bolus dose.

e) Effect on heart rate in conscious rat

The animal is slightly anaestetized by ether and an infusion cannula is inserted into a tail vein. While still asleep the rat is placed in a simple device, made of a coarse, somewhat elastic net fixing the rat in a constant position. Electrodes are attached to the extremities and connected to an ECG-pulse pre-amplifier and a Grass polygraph. By recording the ECG, the heart rate can then be determined.

Before any substance is given the animal has regained consciousness and the heart rate has been constant for at least 15 minutes.

The substance is injected, i.v. in the infusion cannula and flushed with physiological saline.

ECG is recorded 0.25, 0.5, 1, 2, 3 and 5 minutes after completed injection and then every 5 minutes until the original heart rate is obtained.

TABLE 1

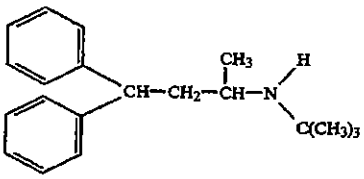
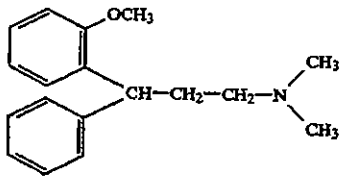
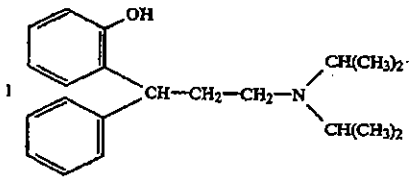
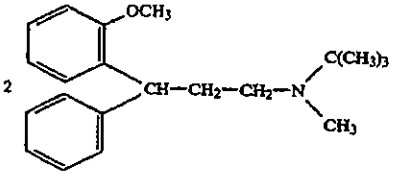
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
 Terodiline (prior art)	5.2×10^{-7}	2.4×10^{-6}	10^{-5}	4×10^{-6}	15-20	20	1-3
 GB-A-1.169.944 (antidepressant)	1.2×10^{-6}	4.4×10^{-6}	2.1×10^{-5}	3.7×10^{-7}	10-15	15	
1  Racemate	1.8×10^{-8}	10^{-5}	1.5×10^{-5}	7×10^{-6}	10-20	20	1-3
1a (+)-isomer of 1	1.8×10^{-8}						
1b (−)-isomer of 1	1.4×10^{-8}						
2 	1.5×10^{-7}	3.5×10^{-6}	9×10^{-6}		10-20	20	

TABLE 1-continued

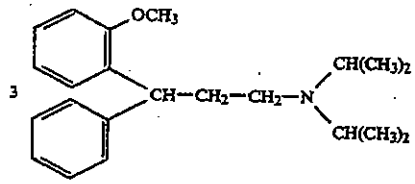
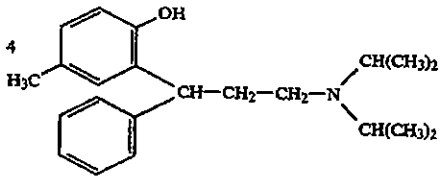
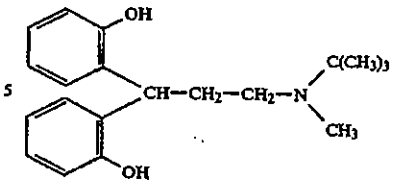
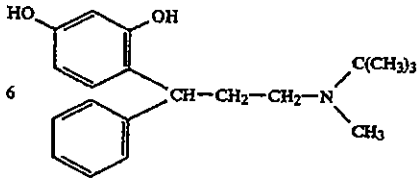
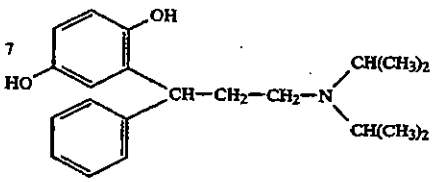
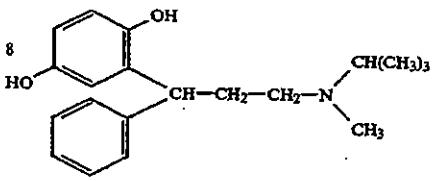
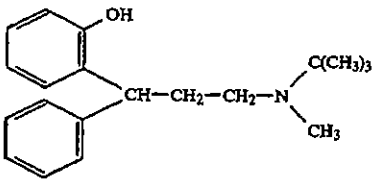
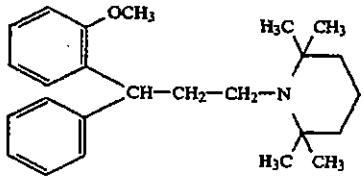
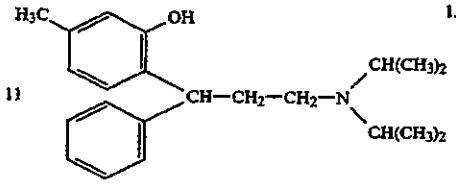
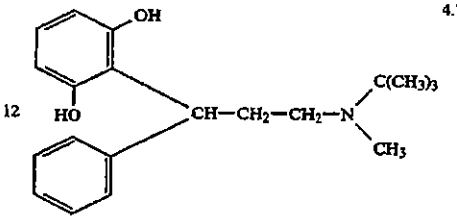
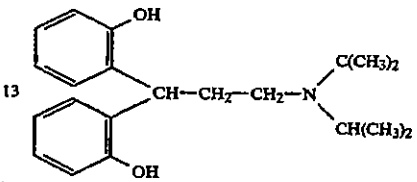
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
3 	2.4×10^{-7}	3.6×10^{-6}	$>10^{-4}$		3–10	10	
4 	1.5×10^{-8}	5.5×10^{-6}	6×10^{-6}	10^{-5}	30–40	40	
4a. (+)-isomer of 4-tartrate	1.3×10^{-8}		6.5×10^{-6}		10–20	20	
4b. (−)-isomer of 4-tartrate	1.3×10^{-6}		6×10^{-6}		10–20	20	
5 	4.9×10^{-9}	3.8×10^{-5}	3×10^{-5}	10^{-5}	30–45	45	1–3
6 	2.0×10^{-7}	3×10^{-5}	6.5×10^{-5}	1.3×10^{-5}	>20	>20	
7 	1.9×10^{-8}	5×10^{-5}	6.5×10^{-5}	3×10^{-6}	30–50	50	
8 	3.1×10^{-8}	5×10^{-5}	$>5 \times 10^{-5}$	7×10^{-6}	>6	>6	

TABLE 1-continued

Substance	Antichol. effect. IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
9 	1.6×10^{-8}	5×10^{-5}	2.5×10^{-5}	1.2×10^{-6}		20	
10 	6.2×10^{-8}	4×10^{-6}	7×10^{-6}	2.5×10^{-6}			
11 	1.0×10^{-8}	5.5×10^{-6}	10^{-5}	2.5×10^{-6}	10-20	20	
12 	4.7×10^{-7}		2.3×10^{-5}	8.0×10^{-6}	15-30	30	
13 	9.0×10^{-9}	3×10^{-5}	1.5×10^{-5}	2×10^{-5}	5-10	10	

EXAMPLE A

Preparation of tablets

Ingredients	mg/tablet
1. Compound 1 in Table 1	2.0
2. Cellulose, microcrystalline	57.0
3. Calcium hydrogen phosphate	15.0
4. Sodium starch glycolate	5.0
5. Silicon dioxide, colloidal	0.25
6. Magnesium stearate	0.75
	80.0 mg

The compound 1 according to the invention is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, the resultant mixture being mixed for about 5 minutes and then compressed into tablet form with or without filmcoating.

EXAMPLE B

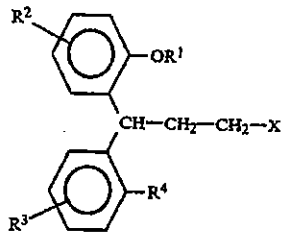
Preparation of capsules

Ingredients	mg/capsule
1. Compound 1 in Table 1	2
2. Lactose	186
3. Corn starch	20
4. Talc	15
5. Magnesium stearate	2
	225 mg

The compound 1 according to the invention is mixed with ingredients 2 and 3 and then milled. The resulting mixture is then mixed with ingredients 4 and 5 and then filled into capsules of appropriate size.

We claim:

1. 3,3-Diphenylpropylamines of formula I



I

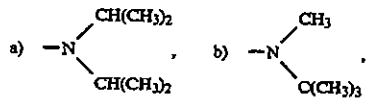
wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II

II

wherein each of R^5 and R^6 independently signifies C_{1-6}alkyl, which may be joined to form a non-aromatic ring having no hetero atom other than the amine nitrogen and each of which may carry a hydroxy substituent, or adamantyl, and wherein R^5 and R^6 together contain at least four carbon atoms, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. 3,3-Diphenylpropylamines according to claim 1, wherein at least one of R^5 and R^6 is C_{1-6}alkyl comprising a branched carbon chain.

3. 3,3-Diphenylpropylamines according to claim 1, wherein X signifies any of the following groups a)–f), each of which may carry a hydroxy substituent:



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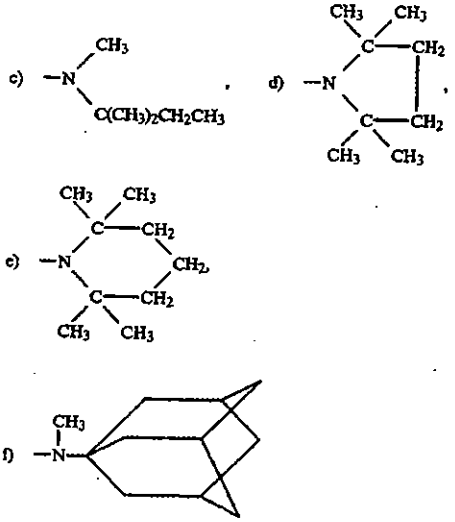

4. 3,3-Diphenylpropylamines according to claim 1, selected from the group consisting of the following compounds, their salts with physiologically acceptable acids and, where possible, their racemates and individual enantiomers: N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine,N-methyl-N-tert-.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine, N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine, N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine, N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine, N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine, N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,N-N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine, N-2,2,6,6-tetramethylpiperdine-,(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, and N,N-diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine.

5. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to claim 1 and a compatible pharmaceutical carrier.

6. The 3,3-diphenylpropylamines of claim 1 being (+)-isomers.

7. The pharmaceutical composition of claim 5 wherein the 3,3-diphenylpropylamine is present in effective anticholinergic amount.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,382,600
APPLICATION NO. : 07/810185
DATED : January 17, 1995
INVENTOR(S) : Jönsson et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, col. 38, line 39:
"N-2,2,6,6-tetramethylpiperdine-" should read
--N-(3-(2-methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine--

Signed and Sealed this

Eighteenth Day of July, 2006

JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT B

(12) **United States Patent**
Nilvebrant et al.

(10) **Patent No.: US 6,630,162 B1**
(45) **Date of Patent: *Oct. 7, 2003**

(54) **PHARMACEUTICAL FORMULATION AND ITS USE**

(75) Inventors: **Lisbeth Nilvebrant**, Bromma (SE); **Bengt Hallen**, Sollentuna (SE); **Birgitta Olsson**, Stenhamra (SE); **Jan Strombom**, Vattholm (SE); **Torkek Gren**, Kalamazoo, MI (US); **Anders Ringberg**, Stockholm (SE); **Martin Wikberg**, Kullavik (SE)

(73) Assignee: **Pharmacia AB**, Stockholm (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/708,428**

(22) Filed: **Nov. 9, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/SE99/02052, filed on Nov. 11, 1999.
(60) Provisional application No. 60/202,862, filed on May 10, 2000.

(30) **Foreign Application Priority Data**

Mar. 9, 2000 (SE) 0000782

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/26; A61K 9/16; A61K 9/22

(52) **U.S. Cl.** **424/458**; 424/457; 424/459; 424/461; 424/462; 424/468; 424/469; 424/490; 424/493; 424/494; 424/495

(58) **Field of Search** 424/457, 458, 424/459, 461, 462, 468, 469, 490, 493, 494, 495

(56) **References Cited**

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5,559,269 A		9/1996	Johansson et al.

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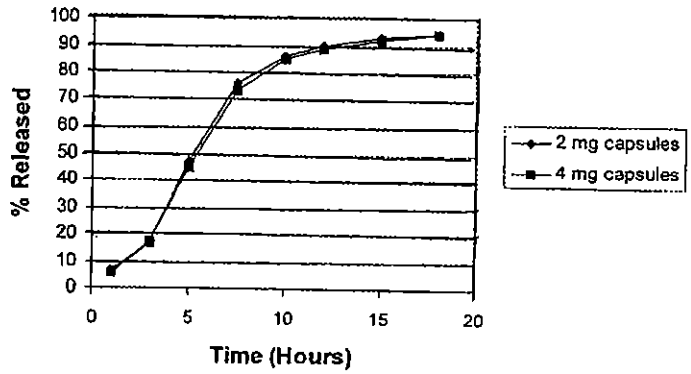
(57) **ABSTRACT**

The invention relates to a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours. The invention also relates to the use of the pharmaceutical formulation for treating overactive bladder and gastrointestinal disorders.

23 Claims, 1 Drawing Sheet



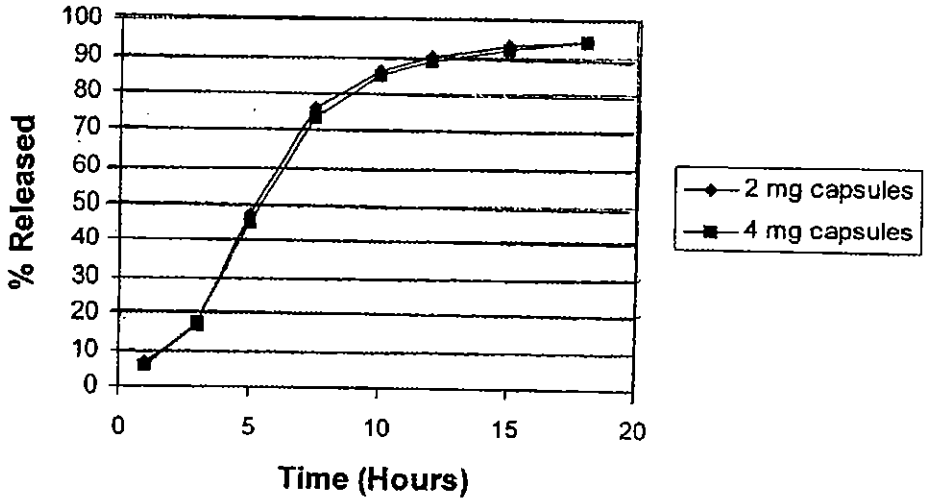

100
90
80
70
60
50
40
30
20
10
0
% Released
0
5
10
15
20
Time (Hours)
2 mg capsules
4 mg capsules

FIG. 1

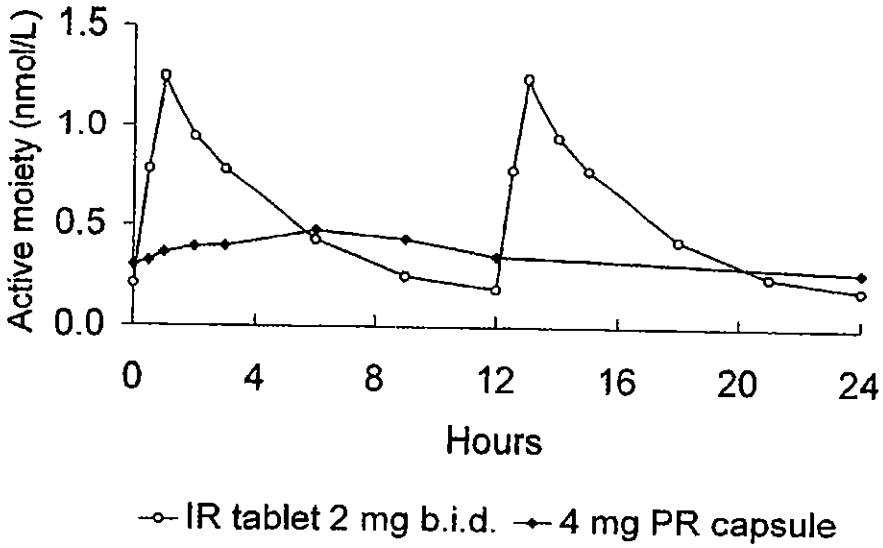

1.5
1.0
0.5
0.0
Active moiety (nmol/L)
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

PHARMACEUTICAL FORMULATION AND ITS USE

This application is a continuation-in-part of PCT international application No. PCT/SE99/02052 which has an international filing date of Nov. 11, 1999 and which designated the United States, the entire contents of which are hereby incorporated by reference. This application also claims priority under 35 U.S.C. 119(e) of U.S. Provisional No. 60/202,862, filed on May 10, 2000, the entire contents of which are also hereby incorporated by reference.

The present invention relates to a pharmaceutical formulation for administering tolterodine or a tolterodine-related compound, and to the medical use of such a formulation.

A substantial part (5–10%) of the adult population suffers from overactive or unstable urinary bladder, often also referred to as urinary incontinence. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. The prevalence of overactive bladder, particularly of so-called urge incontinence, increases with age. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Recently, however, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195–207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647–655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287–295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

Our co-pending international application PCT/SE99/01463 relates to the administration of tolterodine and tolterodine-related compounds through a controlled release formulation and is based on the finding that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

Our above-mentioned PCT/SE99/01463 discloses treatment of overactive bladder by the administration of a controlled release formulation that delivers tolterodine, a tolterodine-related compound, or a pharmacologically acceptable salt thereof such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

The present invention is based on the unexpected observation that a substantially constant serum level of the active moiety or moieties for 24 hours may be obtained through oral administration of a controlled release pharmaceutical formulation that releases the major content of active compound in less than about 18 hours, and more particularly that the formulation has an in vitro release of not less than about 80% after 18 hours at the conditions specified below.

In one aspect, the present invention therefore provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

A second aspect of the invention relates to the use of the pharmaceutical formulation for treating a disorder or disease selected from overactive bladder (including i.a. urinary incontinence and nocturia) and gastrointestinal disorders.

A third aspect of the invention relates to the use of tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, for the preparation of the pharmaceutical formulation of the above first aspect of the invention.

Preferably, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released is not less than about 80% after 15 hours, especially not less than about 80% after 12 hours.

On the other hand, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after 1 hour is preferably not more than about 50%, especially not more than about 30%.

The fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after three hours is preferably from about 30 to 95%, especially from about 40 to about 85%.

It may be preferred that after 7 hours, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 50%, especially not less than about 80%.

In an exemplary in vitro release profile for the pharmaceutical formulation, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50% after 1 hour, from about 30 to about 95% after 3 hours, and more than about 50% after 7 hours.

The in vitro release measurement conditions referred to above are those for a drug release test that utilizes the United

States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deareated phosphate buffer at pH 6.8 and 37° C., where the phosphate buffer solution is prepared as described on pages 2049–2050 in USP 23. The phosphate buffer nominally contains 0.05 M phosphate.

By the term "active moiety or moities" it is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any substantial peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI=(Cmax-Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite) are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

The formulation of the present invention is not restricted to any particular type of formulation. Thus, various types of controlled or sustained release type formufations may be used for embodying the present invention, such as, for example, osmotic tablets, gel matrix tablets, coated beads, etc.

A common type of controlled release formulation that may be used for the purposes of the present invention comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer. A "sealcoat" may be provided between the inert core and the layer containing the active ingredient. When the core is of a water-soluble or water-swellable inert material, the sealcoat is preferably in the form of a relatively thick layer of a water-insoluble polymer. Such a controlled release bead may thus comprise:

(i) a core unit of a substantially water-soluble or water-swellable inert material;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein the first layer is adapted to control water penetration into the core.

The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

Usually, the first layer (ii) above constitutes more than about 2% (w/w) of the final bead composition, preferably more than about 3% (w/w), e.g. from about 3% to about 80% (w/w).

The amount of the second layer (ii) above usually constitutes from about 0.05 to about 60% (w/w), preferably from about 0.1 to about 30% (w/w) of the final bead composition.

The amount of the third layer (iv) above usually constitutes from about 1 to about 50% (w/w), preferably from about 2 to about 25% (w/w) of the final bead composition.

The core unit typically has a size in the range of from about 0.05 to about 2 mm.

The controlled release beads may be provided in a multiple unit formulation, such as a capsule or a tablet.

The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. The cores may be spheres of materials such as sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (dispersed or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the

polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

The above controlled release beads and formulation, respectively may be produced by a method comprising the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient; wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

Optionally, one or more additional polymer layers are applied to the core as has been mentioned above.

The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets.

The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30–80° C., for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35° C. before stopping the process.

As mentioned above, the pharmaceutical formulation according to the present invention may be used for treating, inter alia, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The formulation may also be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

The pharmaceutical formulation according to the present invention has proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urinary incontinence (urge incontinence), urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. the above-mentioned U.S. Pat. No. 5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned U.S. Pat. No. 5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

The invention will now be described in more detail by the following non-limiting Examples. Reference will be made to the accompanying drawings, wherein:

FIG. 1 is a diagram showing the fraction of tolterodine L-tartrate released in vitro versus time for 2 and 4 mg controlled release capsules according to the Example below; and

FIG. 2 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a prede-

termined total dosage of tolterodine (4 mg) through a prolonged release (PR) capsule (4 mg) according to the Example below once daily. The corresponding variation with a prior art immediate release (IR) tablet (2 mg) twice daily is also shown.

EXAMPLE

Preparation of Controlled Release Beads and Capsules

An exemplary bead formulation containing tolterodine L-tartrate as active ingredient has the following structure:

Core:	Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73% w/w of the final bead; purpose: coating substrate;
First layer:	Surelease ® "sealcoat" (Surelease ® is an aqueous film-coating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil), and manufactured by Colorcon, Inc, USA); comprises about 12% w/w of the final bead; purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;
Second layer:	Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3% w/w of the final bead; ratio of Tolterodine:HPMC is 5:1; purpose: drug supply;
Third layer:	Surelease ®/HPMC; comprises about 12% w/w of the final bead; ratio of Surelease ®:HPMC is 6:1; purpose: drug release rate control;

Beads with a three-layer coating having the above characteristics were prepared as follows:

1200 g of sugar spheres, 20–25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40° C. with the following three coating liquids:

(1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;
(2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and
(3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

After tray drying for 3 hours at 70° C., the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20–25 mesh	68.6 mg	137.2 mg
Surelease ®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer:	HPMC; comprises about 1% w/w of the final bead; purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Drug In Vitro Release Study

A drug-release test which utilizes the USP Apparatus 1 (rotating basket) at 100 rpm with 1000 mL of deaerated phosphate buffer prepared at pH 6.8, was used to study the in vitro release at 37° C. of the two three-layered beads-containing 2 and 4 mg capsules prepared above. The buffer was identical to that used for the Buffer Stage testing of Delayed-release dosage forms described in USP 23 General Chapter 724, and nominally contains 0.05 M phosphate and 0.075 M chloride. The results are shown in FIG. 1. As can be seen therein, about 90% of the tolterodine tartrate had been released from both capsules after 12 hours.

Pharmacokinetic Study—Determination of Serum Concentrations of Tolterodine and Main Metabolite

A clinical trial was performed in patients with overactive bladder to determine the pharmacokinetic effects of a (i) a once daily dose of a 4 mg tolterodine controlled release capsule (below referred to as TOD) as described above, and (ii) two doses daily of a tolterodine immediate release tablet (below referred to as TIR), described below. 30 patients were subjected to each of the treatments. The measurements were performed on day seven in each treatment period and included measurements of serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time.

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human 25 serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136). FIG. 2 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily (PR capsule in FIG. 2), and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as $FI=(Cmax—Cmin)/AUC\tau/\tau$, where τ is the length of the dosage interval and $AUC\tau$ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index

for the active moiety was 2.29 (95% CI 1.95–2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59–0.78) for the TOD capsule.

While the invention has been described above with reference to specific embodiments thereof, it is not restricted thereto in any way whatsoever. On the contrary, as will be understood by those skilled in the art, various changes, modifications, substitutions and omissions can be made without departing from the basic concept of the invention as defined in the claims which follow. Thus, for example, other sustained release formulations may be used.

What is claimed is:

1. An oral pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, as active ingredient, wherein said formulation exhibits controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours, and wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as $FI=(Cmax-Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

2. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80% after 15 hours.

3. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80% after 12 hours.

4. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50% after 1 hour.

5. The formulation according to claim 4, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 30% after 1 hour.

6. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 30 to about 95% after 3 hours.

7. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 40 to about 85% after 3 hours.

8. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 50% after 7 hours.

9. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 80% after 7 hours.

10. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not more than about 50% after 1 hour, from about 30 to about 95% after 3 hours, and not less than about 50% after 7 hours.

11. The formulation according to claim 1, wherein the in vitro release is measured by a drug release test which utilizes the United States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deaerated phosphate buffer at pH 6.8 and 37° C., where the phosphate buffer solution is prepared as described on pages 2049–2050 of USP 23, and nominally contains 0.05 M phosphate.

12. The formulation according to claim 1, which comprises tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a salt thereof.

13. The formulation according to claim 1, which comprises tolterodine, or a salt thereof.

14. The formulation according to claim 1, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

15. The formulation according to claim 14, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

16. A method of treating an overactive bladder, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

17. A method of treating urinary incontinence, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

18. A method of treating nocturia, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

19. A method of treating gastrointestinal disorders, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

20. A method for orally administering tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, to a patient to maintain a substantially constant serum level of the active moiety or moieties for 24 hours, which method comprises administering a pharmaceutical formulation containing tolterodine, a tolterodine-related compound or a salt thereof, which formulation exhibits a controlled in vitro release in phosphate buffer at pH 6.8 of tolterodine, tolterodine-related compound or salt thereof of not less than about 80% after 18 hours.

21. The formulation according to claim 1, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

22. The formulation according to claim 15, wherein the 24-hour serum profile, is from about 10 nM*h to about 120 nM*h.

23. The formulation according to claim 16, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

* * * * *

EXHIBIT C

US006770295B1

(12) **United States Patent**
Kreilgård et al.

(10) **Patent No.: US 6,770,295 B1**
(45) **Date of Patent: Aug. 3, 2004**

(54) **THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE**

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(73) Assignee: **Pharmacia AB**, Stockholm (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/582,498**

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§ 371 (c)(1),
(2), (4) Date: **Nov. 14, 2000**

(87) PCT Pub. No.: **WO00/12069**

PCT Pub. Date: **Mar. 9, 2000**

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Nov. 11, 1998 (SE) 9803871

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/52; A61K 9/70; A61F 13/00

(52) **U.S. Cl.** **424/457**; 424/468; 424/449

(58) **Field of Search** 424/449, 457, 424/468, 458, 459, 461, 462

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(74) *Attorney, Agent, or Firm*—Craig M. Bell

(57) **ABSTRACT**

The present invention is drawn to a method of treating an unstable or overactive urinary bladder by treating the patient with tolterodine or a tolterodine-related compound, or pharmaceutically acceptable salt thereof, with a controlled release formulation that maintains a substantially constant serum level of the active moiety or moieties for at least 24 hours. The present invention is further drawn to a formulation for the method.

27 Claims, 2 Drawing Sheets

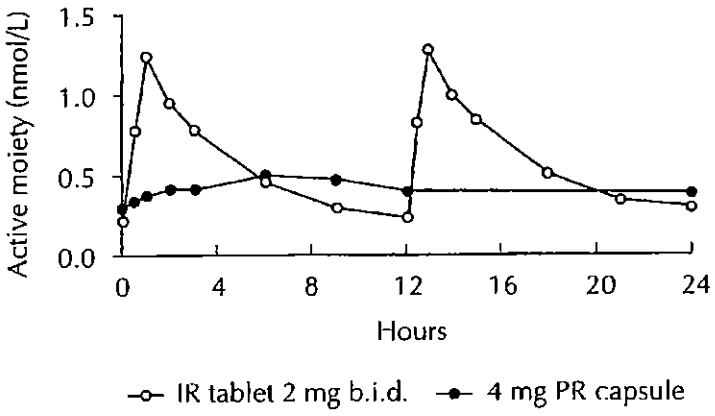


FIG. 1

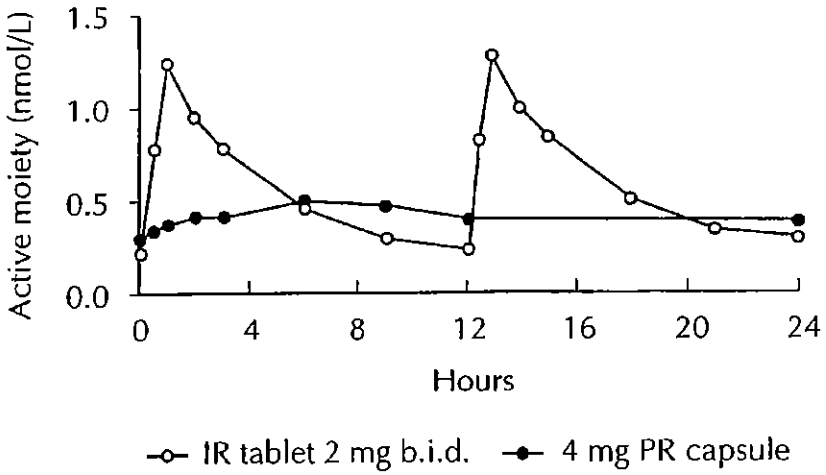

Active moiety (nmol/L)
1.5
1.0
0.5
0.0
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

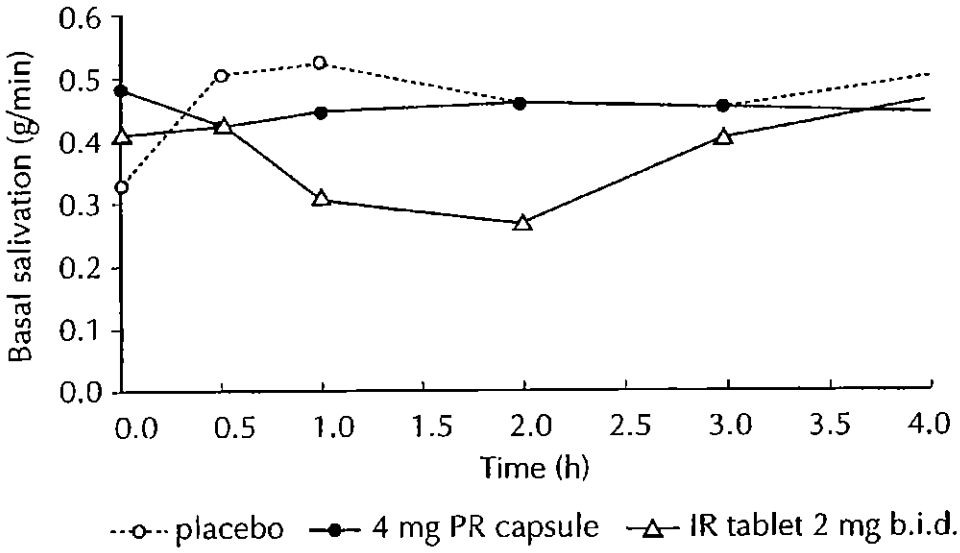
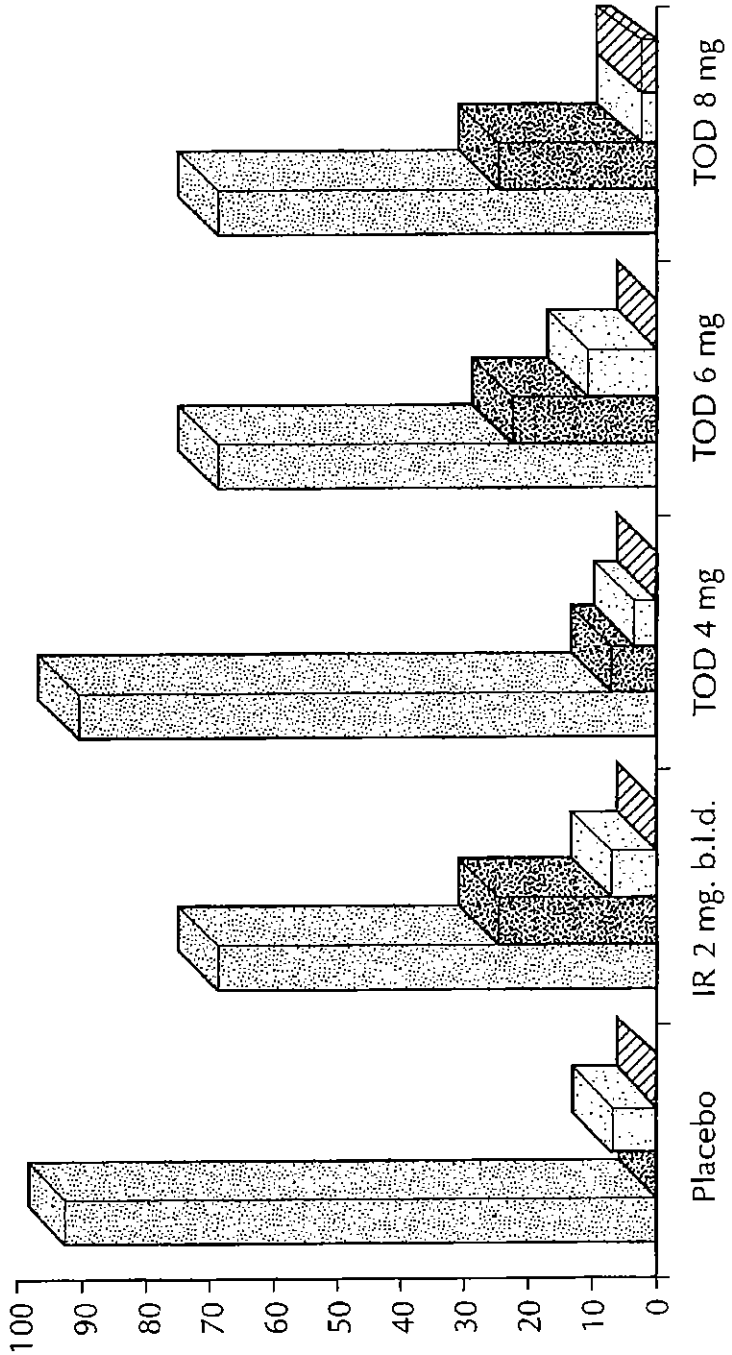

Basal salivation (g/min)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (h)
placebo
4 mg PR capsule
IR tablet 2 mg b.i.d.

FIG. 3


100
90
80
70
60
50
40
30
20
10
0
Placebo
IR 2 mg. b.l.d.
TOD 4 mg
TOD 6 mg
TOD 8 mg

THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

This application is the national phase under 35 U.S.C. §371 of PCT International Application No. PCT/SE99/01463 which has an International filing date of Aug. 26, 1999, which designated the United States of America.

The present invention relates to an improved method of treating unstable or overactive urinary bladder as well as a formulation therefor.

A substantial part (5–10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Oxybutynin, which chemically is the DL-racemic form of 4-diethylamino-2-butynyl-phenylcyclohexylglycolate, is given orally, usually as a tablet or syrup. Oxybutynin, usually administered as the chloride salt, is metabolized to an active metabolite, N-desethyl-oxybutynin. The drug is rapidly absorbed from the gastrointestinal tract following administration and has a duration of from three to six hours. While the effectiveness of oxybutynin has been well documented, its usefulness is limited by classical antimuscarinic side-effects, particularly dry mouth, which often leads to discontinuation of treatment.

WO 96/12477 discloses a controlled release delivery system for oxybutynin, which delivery system is said not only to be of convenience to the patient by reducing the administration to a once daily regimen, but also to reduce adverse side-effects by limiting the initial peak concentrations of oxybutynin and active metabolite in the blood of the patient.

The alleged relief of side-effects by reducing or eliminating peak concentrations through administration of the controlled release delivery system is, however, contradicted by a later published clinical report, Nilsson, C. G., et al., Neurourology and Urodynamics 16 (1997) 533–542, which describes clinical tests performed with the controlled release delivery system disclosed in WO 96/12477 above. In the clinical tests reported, a 10 mg controlled release oxybutynin tablet was compared with the administration of a conventional (immediate release) 5 mg tablet given twice daily to urge incontinent patients. While high peak levels of the drug obviously were eliminated with the controlled release oxybutynin tablet, no difference in side-effects between the controlled release tablet and the conventional tablet was observed. The advantage of the controlled release tablet thus resided merely in enhancing treatment compliance by its once-a-day dosage rather than also reducing side-effects as stated in WO 96/12477.

Recently, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195–207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647–655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287–295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

According to the present invention it has now surprisingly been found that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

In one aspect, the present invention therefore provides a method of treating unstable or overactive urinary bladder, which method comprises administering to a (mammal) patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a controlled rate for at least 24 hours. It is preferred that the dosage form formulation is capable of maintaining a substantially constant serum level of the active moiety or moieties for said at least 24 hours.

Overactive urinary bladder encompasses detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency.

As mentioned above, the chemical name of tolterodine is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine. The term "tolterodine-related compound" is meant to encompass the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms thereof.

By the term "active moiety or moities" is meant the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to

tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the release profile of the controlled release formulation should essentially not exhibit any peak values. This may, more sophistically, also be expressed by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI=(Cmax-Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve) for dosage interval τ, and τ is the length of the dosage interval. Thus, according to the present invention, the controlled release formulation should provide a mean fluctuation index (for n being at least 30) that is usually not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average (blood) serum or plasma levels are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. WO 89/06644. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to WO 94/11337. The (S)-enantiomer and its use in the treatment of urinary and gastrointestinal disorders is described in WO 98/03067.

In another aspect, the present invention provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

Still another aspect of the present invention provides the use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides a controlled release of tolterodine or said tolterodine-related compound, or salt thereof at a controlled rate for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

The controlled release formulation is preferably an oral delivery system or a transdermal preparation, such as a transdermal patch, but also other controlled release forms may, of course, be contemplated, such as buccal tablets, rectal suppositories, subcutaneous implants, formulations for intramuscular administration.

An exemplary type of oral controlled release formulation, a specific embodiment of which is described in Example 1 below, is a multi-unit formulation comprising controlled-release beads. Each bead comprises (i) a core unit of a water-soluble, water-swellable or water-insoluble inert material (having a size of about 0.05 to 2 about 2 mm), such as e.g. a sucrose sphere; (ii) a first layer on the core of a substantially water-insoluble (often hydrophilic) polymer (this layer may be omitted in the case of an insoluble core, such as e.g. of silicon dioxide), (iii) a second layer of a water-soluble polymer having an active ingredient dissolved or dispersed therein, and (iv) a third polymer layer effective for controlled release of the active ingredient (e.g. a water-insoluble polymer in combination with a water-soluble polymer) In the case of an oral controlled release formulation for once-daily administration, the dosage of tolterodine (or tolterodine related compound) is, for example, 4 mg or 6 mg.

A transdermal patch for tolterodine or tolterodine-related compound is described in our co-pending international application "Transdermally administered tolterodine as anti-muscarinic agent for the treatment of overactive bladder" (based on Swedish patent application no. 9802864-0, filed on Aug. 27, 1998), the full disclosure of which is incorporated by reference herein. Illustrative patch formulations are described in Example 2 below.

With the guidance of the disclosure herein, the skilled person may either adapt controlled release administration forms, such as tablets, capsules, patches etc, known in the art, to obtain the objectives of the present invention, or design modified or new controlled release administration forms.

The invention is illustrated by the following Examples, without, however, limiting the scope of the invention in any way. Percentages are by weight, unless otherwise stated. Reference will be made to the accompnaying drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through (i) an immediate release tablet (2 mg) twice daily as in the prior art, and (ii) a controlled release capsule (4 mg) once daily in accordance with the present invention;

FIG. 2 is a diagram showing the variation of the basal salivation (9/min) with time (hours) during 4 hours after administration of (i) a 4 mg tolterodine controlled release capsule in accordance with the present invention, (ii) a prior art tolterodine immediate release tablet, and (iii) placebo; and

FIG. 3 is is a bar chart diagram showing patients' individual estimates of experienced dry mouth side effect (no dry mouth, mild, moderate, severe) after administration of tolterodine through (i) a conventional 2 mg immediate release tablet, (ii) controlled release capsules of 4, 6 and 8 mg, respectively, according to the present invention, and (iii) placebo.

EXAMPLE 1

TOLTERODINE ORAL CR CAPSULE AND IR TABLET

Preparation of Tolterodine CR Capsules 2 mg and 4 mg

A controlled release (CR) capsule containing non-pareil beads coated by (i) an ethylcellulose layer, (ii) a tolterodine/

HPMC layer, and (iii) a sustained release ethylcellulose/HPMC layer was prepared as follows:

1200 g of (starch-containing) sugar spheres, 20–25 mesh, were charged into a Wurster fluid bed and sequentially coated with the following three coating solutions:

(1) a Surelease® sealcoating solution prepared by mixing 788 g of Sureleasee with 563 g of purified water (Surelease® is an aqueous filmcoating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil; manufactured by Colorcon, Inc., West Point, Pa., U.S.A.);

(2) a suspension prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of Hypromellose, 5 cP (hydroxypropylmethyl cellulose (HPMC)); and

(3) a sustained release coating solution prepared by mixing 29 g of Hypromellose, 5 cP, with 375 g of purified water, and then mixing with 695 g of Surelease®.

After drying, the coated spheres were filled into hard gelatin capsule shells (size 3, white/white) to obtain 2 mg and 4 mg capsules, respectively, of the composition (filling mass for 2 mg capsule, 169–207 mg/capsule):

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20–25 mesh	69 mg	137 mg
Surelease ®	21 mg	42 mg
Hypromellose, 5cP	2.0 mg	4.1 mg

Tolterodine L-Tartrate IR Tablets 2 mg

Commercially available tolterodine L-tartate 2 mg tablets for immediate release (IR) (Detrusitol®, Pharmacia & Upjohn AB, Sweden) were used. The tablets had the following composition:

Core	
Tolterodine L-tartrate	2.0 mg
cellulose, microcrystalline	53.4 mg
calcium hydrogen phosphate dihydrate	18.0 mg
sodium starch glycollate	6.0 mg
magnesium stearate	0.4 mg
colloidal anhydrous silica	0.2 mg
Coating	
Methylhydroxypropyl cellulose	1.5 mg
cellulose, microcrystalline	0.3 mg
stearic acid	0.6 mg
titanum dioxide E 171	0.6 mg

PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

A clinical trial was performed in patients with overactive bladder to determine the pharmacodynamic and pharmacokinetic effects of different daily doses of (i) the above described tolterodine controlled release capsule (below referred to as TOD), compared with (ii) the above described tolterodine immediate release tablet (below referred to as TIR), and (iii) a placebo capsule (containing sugar spheres only). The trial was performed as a double-blind, double dummy, cross-over trial in 60 patients for three one week periods and six treatments (2, 4, 6 and 8 mg TOD once daily, 2 mg TIR twice daily, and placebo). All patients were randomised to three out of six treatments, meaning that 30 patients were subjected to each of the treatments. Pharmacodynamic and pharmacokinetic measurements were performed on day seven in each treatment period. The determinations included measurements of (i) serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time, (ii) salivation (dry mouth), and (iii) residual urine volumes.

Serum Concentrations of Tolterodine and Main Metabolite

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136). FIG. 1 shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily, and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI=(Cmax−Cmin)/AUCτ/τ, where τ is the length of the dosage interval and AUCτ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.40 (95% CI 1.95–2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59–0.78) for the TOD capsule.

Salivation (Dry Mouth)

Salivation was measured using dental cotton rolls applied in the mouth for 3×2 minutes. Measurements were performed before breakfast and thereafter after each blood sample on day seven in each treatment period. Based on all measurements after dosing, the mean salivation during 12 hours was calculated. The basal salivation at steady state was measured after treatment with (i) 4 mg TOD capsule, (ii) 2 mg TIR tablet, and (iii) placebo. The results are presented in FIG. 2. As can be seen in the Figure, the salivation is substantially constant during the period shown for the TOD capsule, whereas a considerable reduction in salivation (i.e. drier mouth) is obtained with the TIR tablet.

While FIG. 2 shows the total salivation as measured, the degree of salivation, or dry mouth, was also determined, based on the patient's estimate of experienced intensity of the phenomenon. The results for 2 mg TIR tablet b.i.d., 4 mg TOD capsule, 6 mg TOD capsule and 8 mg TOD capsule, are presented in bar chart form in FIG. 3. The four bars for each dosage represent, from left to right in the figure, no dry mouth, mild, moderate, and severe, respectively.

As apparent from FIG. 2, the dry mouth intensity for the TIR 2 mg b.i.d. tablet is clearly higher than that of the TOD 4 mg capsule, and about twice that dosage, i.e. TOD 8 mg, is required to match the adverse dry mouth effects of the TIR 2 mg b.i.d. tablet.

The results from the salivation determinations thus show that flattening of the concentration peaks of the "active

moiety" (i.e. tolterodine plus 5-HM) leads to a substantial reduction of the undesired dry mouth effect.

Residual Urine Volume

Residual volume is the volume of urine left in the bladder immediately after voiding. Measuring residual volume offers a method of assessing the effect of antimuscarinic treatment on the bladder. In fact, it offers a measure of efficacy (change in residual volume) as well as safety (urinary retention, i.e. inability to pass urine). Efficacy may thus be measured as the mean residual volume per unit of time, and safety as any case where the residual urine exceeds a fixed level. The mean residual volume per micturition was measured by a non-invasive (ultrasonic) method for placebo, TIR tablet 2 mg b.i.d., and for capsules TOD 2 mg, TOD 4 mg, TOD 6 mg, and TOD 8 mg.

The results are presented in Tables 1 and 2 below. Table 1 shows the mean residual volume per micturition, and Table 2 shows the maximum residual volume during 12 hours.

The results presented clearly demonstrate that the TOD capsule dosages are as efficacious as the corresponding TIR b.i.d dosages, and also that the TOD dose may be increased up to 8 mg daily and still be safe with regard to urinary retention.

TABLE 1

Mean Residual Volume per micturition (ml)

	Placebo	TIR 2 mg b.i.d	TOD 2 mg	TOD 4 mg	TOD 6 mg	TOD 8 mg
Estimated mean	29	62	40	59	69	77
95% confidence interval	12 to 46	45 to 79	26 to 55	51 to 66	60 to 78	65 to 89
Estimated difference vs. IR			−22	−4	7	14
			−44 to 1	−23 to 15	−15 to 26	−7 to 36

TABLE 2

Maximum Residual Volume during 12 hours

	Placebo	TIR 2 mg b.i.d	TOD 2 mg	TOD 4 mg	TOD 6 mg	TOD 8 mg
Median value (ml)	46	72	45	55	87	77
min–max	5–267	10–316	0–192	0–249	0–360	0–390

The results from the clinical trial described above demonstrate that a flatter serum concentration of active moiety (tolterodine plus 5-HM) not only does not lead to a loss of efficacy or to untoward side-effects, primarily urinary retention, but, importantly, also provides for a reduced dry mouth effect (unaffected or less reduced salivation).

EXAMPLE 2

TOLTERODINE TRANSDERMAL PATCH FORMULATION

Tolterodine-releasing patches were prepared as follows:

System 1 (Drug-in-Adhesive, Acrylate)

5 g of tolterodine base were dissolved in 11 g of ethanol and added to 20 g of Durotak 387-2287 (National Starch & Chemical, U.S.A.). The drug gel was coated onto a backing membrane (Scotchpak 1012; 3M Corp., U.S.A.) by using a coating equipment (RK Print Coat Instr. Ltd, Type KCC 202 control coater). The wet layer thickness was 400 μm. The laminate was dried for 20 min. at RT and then for 30 min. at 40° C. A polyester release liner (S 2016; Rexam Release) was laminated onto the dried drug gel. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,5 mg/cm^2.

System 2 (Multi-laminate, Acrylate)

5 g of tolterodine base were dissolved in 10 ml of ethanol. A mix of 6,4 g of Eudragit RL 100 (Röhm GmbH Chemische Fabrik, Germany) and 6,4 of ethanol and a mix of 2,6 g of Polyvidone 90 (BASF, Germany) and 10,2 g of ethanol were added to the solution of tolterodine base in ethanol. Finally, 4 g of propylene glycol were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment above. The wet layer thickness was 400 μm. The laminate was then dried at 40° C. for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80° C. for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,0 mg/cm^2.

System 3 (Multi-laminate Water-based Acrylate)

1 g of tolterodine base was mixed with Tween 80 (Merck) by heating to 60–70° C. 1,8 g of triethylacetate and 1,3 g of dem. water was added to the mix. The final mix was then added to 25 g of Eudragit RL 30 D (Röhm GmbH Chemische Fabrik, Germany). Finally, 180 mg of 1 N NaOH were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment. The wet layer thickness was 400 μm. The laminate was dried at 40° C. for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80° C. for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 0,5 mg/cm^2.

What is claimed is:

1. A method of treating unstable or overactive urinary bladder, wherein the method comprises administering to a patient in need of such treatment tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through a controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or moieties for at least 24 hours, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

2. The method according to claim 1, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as FI=(Cmax−Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

3. A method of treating unstable or overactive urinary bladder, wherein the method comprise administering to a patient in need of such treatment tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through controlled release formulation capable of maintaining a

substantially constant serum level of the active moiety or moieties for at least 24 hours with reduced undesirable side effects and with no reduction in the efficacy of the tolterodine compound, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

4. The method according to claim 1, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

5. The method according to claim 1 wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

6. The method according to claim 1, wherein the controlled release formulation is a transdermal preparation.

7. The method according to claim 1 wherein tolterodine is administered.

8. The method according to claim 1 wherein urinary incontinence is treated.

9. A pharmaceutical formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

10. The formulation of claim 9, which provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as $FI=(Cmax-Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

11. A pharmaceutical formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of said tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or pharmaceutically acceptable salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours for efficacious therapy with reduced undesirable side effects, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

12. The formulation according to claim 9, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

13. The formulation according to claim 9, which is a capsule or tablet for oral administration once daily.

14. The formulation according to claim 1, which is a transdermal preparation.

15. The formulation according to claim 9, which provides controlled release of tolterodine.

16. The method of claim 3, wherein the controlled release formulation is administered orally.

17. The formulation of claim 11, which is in a form for oral administration.

18. The method according to claim 2, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

19. The method according to claim 3, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 10 nM*h to about 120 nM*h.

20. The method according to claim 4, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

21. The method according to claim 6, wherein the transdermal preparation is a transdermal patch.

22. The formulation of claim 10, wherein the mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

23. The formulation according to claim 11, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 10 nM*h to about 120 nM*h.

24. The formulation according to claim 12, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

25. The transdermal preparation of claim 14, which is a transdermal patch.

26. The method of claim 3, wherein increased efficacy of the tolterodine compound is obtained with minimal undesirable side effects.

27. The formulation of claim 11, wherein increased efficacy of the tolterodine compound is obtained with minimal undesirable side effects.

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